Women Health, Maternal Health and HIV infection in West Africa

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Santé de la femme, Santé Maternelle et infection par le VIH en Afrique de l'Ouest

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To the loving memory of my Mother, my Aunt and my Grandmother

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*"Nothing new can come into our lives unless we're **grateful** for what we already have…"*

Abstract

HIV infection in sub-Saharan Africa is a major public health threat particularly for girls and women of reproductive age. The research presented in this thesis was conducted particularly in West Africa and the specific objectives are i) to estimate the prevalence of intimate partner violence according to HIV serological status; ii) to estimate the incidence rate of pregnancy following ART initiation; iii) to determine the effect of pregnancy after ART initiation on the risk of death, HIV-disease progression and loss to follow-up. Firstly, in Togo, According to our findings, the prevalence rates of lifetime physical and sexual violence (IPV) among HIV-infected women were significantly higher than among uninfected women (63.1 vs. 39.3%, p=0.01 and 69.7 vs. 35.3%, p=0.01, respectively). Secondly, Among HIV-infected West African women, the crude incidence of first pregnancy after ART initiation was 2.9 per 100 women-years [95% confidence interval (CI): 2.7 to 3.0] and it could be as high as 4.7 per 100 women-years (95% CI: 4.3 to 5.1) among women aged 25-29 years old. Finally, pregnancy after ART initiation appeared to reduce the risk of death or HIV-disease progression (Adjusted Hazard Ratio [aHR] =0.61; 95%CI: 0.40-0.92) and the risk of becoming LTFU at M48 (aHR=0.74; 95%CI: 0.60-0.92) among West African HIV-infected women. Intimate partner violence is highly prevalent among HIV-infected women and it may have negative repercussions on their health status. Pregnancy is a common event after ART initiation and it might have repercussions on the health status of HIV-infected women. The design of safe motherhood programs addressed to HIV-infected women and its integration within HIV care services must are a public health priority in sub-Saharan Africa.

Résumé

En Afrique sub-Saharienne, les femmes et les filles sont particulièrement vulnérables à l'infection par le VIH. L'infection par le VIH est une menace importante pour la santé reproductive de cette population. Les études de recherche présentées dans le cadre de cette thèse ont été conduites en Afrique de l'Ouest et avaient pour objectifs principaux : i) Estimer la prévalence de la violence perpétrée par le partenaire intime selon le statut sérologique ; ii) Estimer l'incidence de grossesse après la mise sous traitement antirétroviral ; iii) Déterminer l'effet de la grossesse après la mise sous ARV sur le risque de décès, de progression de la maladie à VIH et d'être perdu de vue. Nos résultats nous montrent que la prévalence de violence physique et sexuelle perpétrée par le partenaire intime est plus élevée auprès des femmes VIH-positives qu'auprès de celles non-infectées (63,1 vs. 39,3%, p=0.01 and 69,7 vs. 35,3%, p=0.01, respectivement). De plus, l'incidence brute globale de première grossesse après la mise sous ARV en Afrique de l'Ouest est de 2,9 par 100 femmes-années (IC95% :2,7 – 3,0). Auprès des jeunes femmes âgées de 25-29 ans cette incidence peut être de 4,7 per 100 femmes-années (IC95% :4,3 – 5,1). Finalement, la grossesse après la mise sous ARV réduit le risque de décès ou de progression de la maladie à VIH (aHR : 0,61, CI95% : 0,40-0,92) ainsi que le risque de devenir perdue de vu (aHR : 0,74 ; CI95% : 0,60-0,92) des femmes ouest-africaines infectées par le VIH. La prévalence de violence perpétrée par le partenaire intime est très élevée auprès des femmes infectées par le VIH et cela pourrait entrainer des conséquences négatives de santé de ces femmes. La grossesse est un évènement fréquent auprès des femmes VIH positives sous ARV qui a des répercussions importantes sur le statut de santé des femmes séropositives. L'intégration des programmes de prise en charge maternelle dans les services de prise en charge du VIH doit être priorisé en Afrique sub-saharienne.

Résumé en français

Historique épidémiologique de la féminisation de l'épidémie de VIH au niveau mondial

L'épidémie du virus de l'immunodéficience humaine (VIH) est considérée parmi les plus grandes catastrophes de santé publique de l'histoire de l'humanité. Depuis son apparition, 75 millions de personnes ont acquis l'infection par le VIH et l'infection par ce virus a été responsable de 36 millions de décès au niveau mondial. Trente ans depuis le premier cas confirmé de VIH et malgré les grands efforts déployés pour ralentir la progression de l'épidémie, un nombre important de nouvelles infections sont rapportées encore chaque année et le VIH est encore une cause majeure de décès dans le monde.

En 2013, Il a été estimé qu'un total de 35,3 millions de personnes vivaient avec le VIH au niveau mondial, et parmi elles 2,3 millions avaient nouvellement acquis l'infection au cours de cette année. L'Afrique sub-saharienne, hébergeant environ trois quarts de la population vivant avec le VIH au niveau mondial, est la région du monde la plus touchée par la pandémie. Ainsi, en 2013, le nombre de personnes vivant avec le VIH dans cette région du monde s'élevait à 23,5 millions. En Afrique sub-Saharienne, pendant cette même année, environ 1,6 millions de nouvelles infections par le VIH ont été diagnostiquées, soit 70% du total des nouvelles infections par le VIH au niveau mondial.

Au début de l'épidémie, les hommes étaient la population la plus affectée par le VIH, essentiellement ceux qui entretenaient des relations sexuelles avec d'autres hommes. Puis le visage de l'épidémie a changé, sa propagation ne se limitant plus aux seuls homosexuels masculins, et la distribution par genre de l'épidémie s'est ainsi ensuite inversée à partir de la fin du dernier siècle. On a ainsi commencé à parler d'une féminisation de l'épidémie d'infection par le VIH.

Cette féminisation de l'épidémie d'infection par le VIH était tout particulièrement marquée en Afrique sub-Saharienne où 60% de la population vivant avec le VIH était constituée des femmes. Cette prévalence était d'autant plus élevée auprès des jeunes âgées entre 15 et 24 ans vivant avec le VIH, parmi lesquels les femmes représentaient 75%. Au début des années 2000, les jeunes femmes africaines âgées entre 15 et 24 ans avaient une probabilité d'être infectée par le VIH huit fois plus élevé que n'importe quelle autre population du même âge au niveau mondial. L'épidémie à VIH est ainsi un problème majeur de santé publique en

Afrique sub-saharienne, et ce tout particulièrement pour les jeunes femmes et les femmes en âge de procréer.

Contexte actuel mondial de l'épidémie d'infection à VIH

Au cours des dernières années, des avancées scientifiques considérables ont permis de contrôler puis réduire l'expansion de cette épidémie. Des réductions importantes des taux d'incidence ont notamment été observées dans les contextes les plus touchés par la pandémie. L'expansion à l'échelle universelle de l'accès aux médicaments antirétroviraux a permis aux personnes vivant avec le VIH d'améliorer considérablement leur espérance de vie, leur qualité de vie et de réduire leur infectiosité à leurs partenaires sexuels.

Cependant et malgré tous ces avancés, l'Afrique sub-saharienne reste toujours la région du monde la plus touchée par l'épidémie de VIH. De même, les femmes en âge de procréer constituent toujours la population la plus vulnérable à acquérir ce virus dans le contexte africain. De plus, les femmes se trouvent au carrefour de la transmission du virus, tant étant les plus vulnérables à acquérir l'infection par le VIH par voie sexuelle, mais aussi tout en étant le véhicule de l'épidémie pédiatrique par la voie verticale.

En termes de santé publique, les femmes enceintes infectées par le VIH ont été la cible d'un nombre important d'interventions préventives. Ces interventions ont été dirigées notamment vers la réduction du risque de transmission du VIH de la mère à l'enfant pendant la grossesse, autour de l'accouchement et au cours de la pratique de l'allaitement maternel. Néanmoins, l'effet du traitement antirétroviral sur la santé sexuelle et reproductive des femmes vivant avec le VIH en âge de procréer a été peu étudié, et ce tout particulièrement dans le contexte de l'Afrique de l'Ouest.

Vulnérabilité des femmes face à l'infection par le VIH

Les femmes ont ainsi une vulnérabilité particulièrement élevée d'acquérir l'infection par le VIH. Cette vulnérabilité des femmes face à l'acquisition de ce virus a été expliquée par une conjonction de facteurs de risque d'ordre à la fois biologique et psychosocial.

La configuration anatomique des organes génitaux féminins ainsi que les mécanismes d'action des hormones sexuelles féminines sur ces organes sont des facteurs biologiques majeurs associés à un risque plus élevé de contracter l'infection par le VIH.

Certains facteurs psychosociaux comme par exemple l'éducation ont été ainsi associés à une vulnérabilité des femmes à acquérir l'infection par le VIH. L'accès à l'éducation permet aux individus de développer des capacités cognitives leur permettant de mieux saisir les messages préventifs et de les intégrer à leurs pratiques d'une manière plus efficace. Il a aussi été souligné que pour les femmes en particulier, le fait d'avoir des attentes professionnelles bien définies réduit le risque de rapports sexuels non protégés, tout en évitant le risque des grossesses non-planifiées et ainsi par ricochets le risque d'acquérir des infections sexuellement transmissibles (IST) tels que le VIH.

Cependant, dans des milieux où l'accès à l'éducation n'est pas universel, les femmes sont parfois contraintes à s'orienter vers le mariage comme une manière d'assurer leur avenir et/ou leur statut social. On observe ainsi qu'en Afrique sub-saharienne, pour des raisons culturelles ou économiques, les femmes ont tendance à choisir des hommes plus âgés qu'elles. Ceci a des conséquences directes sur la dynamique d'acquisition de l'infection par le VIH, puisqu'il a été estimé que les femmes en couple avec des hommes âgés d'au moins cinq ans de plus qu'elles ont un risque plus élevé de contracter l'infection par le VIH au sein de leur couple. Ce risque plus élevé est expliqué d'une part par le fait que chez les hommes, la probabilité d'être infecté par le VIH augmente proportionnellement avec leur âge, et d'autre part, par la capacité limité des jeunes femmes de négocier des rapports sexuels protégés avec leurs partenaires plus âgés. Finalement, le déséquilibre dans les rapports de pouvoir, fréquemment retrouvé dans ces types de relations, peuvent même *in fine* inciter à des actes de violence envers la femme.

Il a ainsi été estimé que, de toutes les formes de violence envers les femmes, la violence perpétrée par le partenaire intime est la forme la plus fréquente. Selon les résultats d'une enquête conduite par l'Organisation Mondiale de la Santé, les prévalences globales de violence physique et sexuelle perpétrée par le partenaire intime peuvent être aussi élevées que 61% et 59% respectivement.

De plus, ces actes de violence perpétrés par le partenaire intime sont associés à des conséquences néfastes pour la santé physique et mentale des femmes, comme par exemple celui de contracter l'infection par le VIH. Il a ainsi été estimé que les femmes victimes de

violence de la part de leur partenaire intime ont 55% plus de risque d'acquérir l'infection par le VIH.

Par ailleurs, il a été suggéré que les femmes séropositives au VIH ont un risque plus élevé d'être victimes de violence physique et sexuelle de la part de leur partenaire intime. Cependant, même si un nombre important d'études ont estimé la prévalence de violence physique et sexuelle perpétrée par le partenaire intime en Afrique sub-saharienne, cette prévalence est peu connue en Afrique de l'ouest, notamment auprès des femmes infectées par le VIH.

Incidence de grossesse après l'initiation du traitement antirétroviral

L'accès universel aux antirétroviraux a amélioré considérablement le statut de santé des individus infectés par le VIH. Cette amélioration significative de la qualité et de l'espérance de vie a changé sans doute leur avis sur la procréation suite à la découverte de leur statut vis-à-vis de l'infection par le VIH. Les études les plus récentes montrent que, même si la proportion d'individus infectés par le VIH rapportant un désir positif de procréation est inférieure à celle des individus non-infectés, ce désir est présent et persistant, et ce tout particulièrement auprès des personnes sous traitement antirétroviral. Auprès des femmes infectées par le VIH, l'âge apparait comme un facteur majeur associé au désir positif de procréer. Le désir de procréation diminue proportionnellement avec l'âge biologique des femmes. Chez ces mêmes femmes, le fait d'être en couple prédit le désir positif de procréer.

La grossesse n'est pas un évènement rarement détecté auprès des femmes infectées par le VIH. Selon la littérature scientifique récente, même si l'incidence de grossesse auprès des femmes infectées par le VIH reste au global inférieure à celle observée chez les femmes non-infectées, cet indicateur épidémiologique reste élevé auprès des femmes infectées sous traitement antirétroviral. De plus, plusieurs études soulignent que cette incidence de grossesse après la mise sous traitement antirétroviral augmente proportionnellement avec le temps passé sous traitement. Ce phénomène suggère un potentiel effet positif du traitement antirétroviral sur les fonctions reproductives.

L'incidence de grossesse a été documentée chez les femmes infectées par le VIH dans plusieurs études scientifiques menées en Afrique sub-saharienne, et les taux rapportés

allaient de 4,4 jusqu'à 24,6 grossesses pour 100 femmes-années. Néanmoins, en Afrique de l'ouest, l'incidence de grossesse auprès des femmes infectées par le VIH suite à la mise sous traitement ARV a été très peu documentée, et ce tout particulièrement depuis le passage à l'échelle des traitements antirétroviraux. .

Mortalité maternelle et infection par le VIH

Etant donné que la grossesse n'est pas un événement isolé après la mise sous traitement en Afrique, on peut se demander si la grossesse peut entrainer un effet négatif sur la santé des femmes infectées par le VIH et traitées.

On sait déjà que l'infection par le VIH a été identifiée comme une cause majeure de mortalité maternelle puisque les femmes enceintes infectées par le VIH ont huit fois plus de risque de décéder que leurs analogues non-infectées. Cependant, les résultats des études menées en Afrique sub-saharienne ayant pour objectif d'explorer l'association de la grossesse avec la mortalité et la progression de la maladie à VIH sont contradictoires et ne permettent pas de conclure à la question posée. Ainsi, certaines études menées en Afrique australe concluent que la grossesse suite à la mise sous traitement antirétroviral apparait comme un facteur protecteur contre le risque de décéder ou de progresser dans la maladie à VIH, tandis que d'autres études menées en Afrique de l'est mettent en évidence un risque plus élevé de décéder associé à la survenue de grossesse après la mise sous traitement. Cette question de recherche n'a pas été explorée en Afrique de l'ouest jusqu'à présent.

Objectifs de thèse

La recherche conduite dans mon parcours doctoral porte sur l'étude de la vulnérabilité de la femme africaine face à l'épidémie de VIH en s'intéressant notamment aux problématiques des violences perpétrées par le partenaire intime, de l'incidence des grossesses dans un contexte d'accès aux traitements antirétroviraux et aux répercussions de la grossesse suite à la mise sous traitement sur la santé maternelle. Les objectifs principaux de mon parcours doctoral étaient donc les suivants :

1. Estimer la prévalence de violences physiques et sexuelles perpétrées par le partenaire intime auprès des femmes infectées par le VIH au Togo ;

2. Estimer l'incidence de grossesse auprès des femmes infectées par le VIH sous traitement antirétroviral dans huit pays d'Afrique de l'Ouest ;
3. Etudier l'association entre la grossesse et le risque de décès, de progression de la maladie à VIH et d'être perdue de vue dans huit pays d'Afrique de l'Ouest.

Objectif 1. Vulnérabilité des femmes face à l'infection par le VIH : Prévalence de violences physiques et sexuelles selon le statut sérologique VIH auprès des femmes togolaises

Nous avons conduit une étude qui a eu pour objectif d'estimer la prévalence de violences physiques et sexuelles auprès des femmes selon le statut sérologique du VIH. Cette étude a été conduite à Lomé au Togo . Nous avons enquêté un total de 454 femmes (150 femmes VIH négatives et 304 femmes VIH positives). Dans cette étude, la prévalence de violence physique et sexuelle perpétrée par le partenaire était significativement plus élevée chez les femmes infectées par le VIH qu'auprès des femmes non-infectées (63,1 vs. 39,3%, p=0,01 et 69,7 vs. 35,3%, p=0,01, respectivement). De plus cette étude a montré aussi que indépendamment du statut sérologique VIH, un risque plus élevé de violence était associé avec le fait d'avoir un partenaire ayant plusieurs partenaires sexuels et avec pour les femmes une entrée précoce dans la vie sexuelle.

Cette étude nous a permis de conclure en soulignant que même si la violence physique et sexuelle perpétrée par le partenaire intime est globalement élevée au Togo, elle est d'autant plus élevée auprès des femmes infectées par le VIH. Ces résultats soulèvent l'importance d'évaluer systématiquement le risque de violence auprès des femmes infectées par le VIH dans les services de prise en charge du VIH.

Objectif 2. Incidence de grossesse suite à la mise sous traitement antirétroviral et ses facteurs associés dans huit pays de l'Afrique de l'Ouest.

Cette étude a été conduite dans le cadre de la collaboration IeDEA West-Africa qui est conduite dans huit pays d'Afrique de l'Ouest. La population de cette étude a été constituée de toutes les femmes ayant moins de 50 ans à la mise sous traitement et ayant initié le traitement antirétroviral entre 1998 et 2011.

Un total de 29.425 femmes VIH-positives sous traitement antirétroviral ont été incluses dans l'analyse et leur âge moyen était de 33 ans (IQR : 28-38) à l'inclusion. Cette population a contribué à 84.870 femmes-années de suivi. L'incidence brute de première grossesse était

de 2,9 pour 100 femmes-années (ICà95% : 2,7 – 3,0). L'incidence de grossesse auprès des femmes âgées en 25 à 29 ans à la mise sous traitement était de 4,7 pour 100 femmes-années de suivi (ICà95% : 4,3 – 5,1). La probabilité de tomber enceinte au cours des quatre premières années de suivi était de 10,9% (ICà95%: 10,4 – 11,4) au global. Chez les femmes âgées entre 20 et 29 ans au moment de l'initiation du traitement antirétroviral, cette probabilité était de 28,4% (ICà95% : 26,3 – 30,6).

Les résultats de cette étude nous permettent de constater que l'incidence de grossesse après la mise sous traitement est élevée, notamment auprès des femmes de moins de 30 ans à la mise sous traitement. Elle souligne tout particulièrement les manques en soins de santé sexuelle et reproductive dans le contexte ouest-africain.

Objectif 3. Association de la grossesse après l'initiation du traitement antirétroviral la rétention dans les soins, la progression de la maladie à VIH, le risque de décès et la réponse immunologique en Afrique de l'Ouest

Cette étude a été conduite sur une base de données rétrospective issue de la cohorte IeDEA West Africa. Dans l'analyse nous avons inclus toutes les femmes âgées de moins de 50 ans, ayant initié leur traitement antirétroviral pour leur propre santé sur une période de dix ans. L'effet de la grossesse (variable dépendante du temps) sur la mortalité à 48 mois de l'initiation du traitement, la progression de la maladie et la perte de vu a été estimé à partir des modèles de Cox. Pour cette première analyse toutes les femmes ayant initié un traitement pendant la grossesse ou présentant un stade SIDA au moment du diagnostic de l'infection par le VIH ont été exclues. Dans une deuxième analyse, le gain moyen de lymphocytes CD4 durant les 24 premiers mois après l'initiation du traitement antirétroviral a été estimé à partir d'un modèle linéaire mixte.

Pour la première analyse un total de 12.851 femmes VIH positives ont été retenues, parmi lesquelles 864 (6,7%) ont reporté au moins une grossesse dans les 48 mois qui suivaient la mise sous traitement antirétroviral. Parmi les femmes étant tombées enceintes, 15,2% avait progressé vers un stade SIDA ou été décédées et 8.3% étaient perdues de vu. Parmi les femmes n'étant jamais tombées enceintes pendant la période d'étude, 12,7% avait progressé vers un stade SIDA ou étaient décédées et 24,8% étaient perdues de vue. Suite à un ajustement sur le niveau de CD4 au moment de l'initiation du traitement, l'âge, l'index de

masse corporel et l'hémoglobine, la grossesse réduisait le risque de progression de la maladie ou de décès (aHR : 0,61 ; ICà95% : 0.40-0.92) et le risque d'être perdu de vue (aHR : 0,71 ; ICà95:0,40 -0,92).

Pour la deuxième analyse, un total de 20.408 femmes VIH-positives ont été retenues, parmi lesquelles 1.561 (6,2%) avait reporté au moins une grossesse dans les 24 mois qui suivaient la mise sous traitement antirétroviral. Le gain moyen de lymphocytes CD4 entre la mise sous traitement et le vingt-quatrième mois après la mise sous traitement était significativement plus élevé parmi les femmes qui avaient rapporté une grossesse pendant les six premiers mois après la mise sous traitement par rapport à celles qui ne sont pas tombées enceintes au cours de la même période

Conclusion

Les résultats des études conduites dans le cadre de mon parcours doctoral m'ont permis de constater premièrement que la violence physique et sexuelle est un phénomène très répandu en Afrique de l'Ouest. Ces résultats montrent aussi que ce phénomène est d'autant plus fréquent auprès des femmes séropositives. Cette étude est la première étude de type épidémiologique menée dans la région mesurant la prévalence des violences physiques et sexuelles auprès des femmes séropositives. Cependant, le schéma d'étude transversal nous permettant de mesurer la prévalence des violences, est une limite majeure pour induire l'association causale de ce phénomène et l'infection par le VIH en Afrique de l'Ouest.

J'ai pu constater également que la grossesse n'est pas un évènement rare auprès des femmes ouest-africaines infectées par le VIH suite à la mise sous traitement antirétroviral. Cette incidence augmente proportionnellement avec le temps de mise sous traitement antirétroviral et elle est d'autant plus élevée auprès des femmes âgées de moins de 30 ans à la mise sous traitement. De même, nous avons constaté que la survenue d'une grossesse après la mise sous traitement antirétroviral n'est pas associée à une augmentation du risque de décéder, de progresser dans la maladie à VIH ou d'être perdu de vue. De plus, la grossesse parait bien avoir des répercussions sur la réponse immunologique des femmes infectées par le VIH, mais ces répercussions ne semblent pas négatives. Ces études sont les premières menées dans la région Ouest-africaine estimant l'incidence de grossesse et les répercussions de celle-ci sur la santé de la femme infectée par le VIH après la mise sous

traitement antirétroviral. Cependant, l'interprétation de ces résultats est limitée par le fait que dans la base de données régional IeDEA West-Africa, les grossesses ne sont pas répertoriées exhaustivement et celles qui sont répertoriées ne sont pas complètement documentées. Au-delà de ce parcours doctoral, j'entends maintenant continuer mes recherches sur cette thématique, en construisant dans le cadre de mon post-doctorat une véritable cohorte prospective qui me permettra de limiter ces biais.

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Albert Minga, ***Juan Burgos-Soto***, Eric Balestre, Benson Okwara, Moussa Y. Maïga, Akouda Patassi, Eugène Messou, Christian Wejse, François Dabis, Renaud Becquet. Association of pregnancy post-ART initiation with retention in care, AIDS, death and immune recovery. ***(Young Investigator Award)***. XXI Conference on retroviruses and Opportunistic Infections. 3-6 March, 2014. Boston, USA.

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1. Introduction

In the history of humanity, the epidemic of Human Immunodeficiency Virus (HIV) has been the most devastating health catastrophe so far. Since the beginning of the epidemic, almost 75 million people have been infected with the HIV virus and about 36 million people have died of HIV worldwide(1). No region in the world has been spared, and HIV has become the most globalized epidemic in human history.

Despite the massive global effort deployed to stop and hold back the progression of the epidemic, HIV claims still for an important number of new infections every year and remains one major cause of death. Current estimations point out that roughly 35.3 million people are living with HIV worldwide and around 2.3 million of new infections occurred during last year 2013(2). Although the number of death has considerably declined during last years since the roll-out of antiretroviral therapy (ART), HIV infection is still responsible for 1.7 million deaths every year worldwide(2).

Although HIV epidemic is considered major global health challenge, it has impacted deeply and negatively resource-limited settings. Sub-Saharan Africa, the most impoverished region of the world has been particularly ravaged by HIV epidemics, hosting the vast majority of HIV-infected individuals. Additionally to the biological factors linked to transmission, the deep inequality at structural, societal and individual levels were major contributors to the rapid and large spread of the epidemic in this region of the world.

In the cusp of the fourth decade of its debut and despite the huge effort delivered to control its progression, HIV remains one major public health challenge, particularly in low-middle income countries and, one major barrier to achieve Millennium Development Goals within these contexts(3, 4). Although one of the Millennium Development Goals (Goal 6) specifically addresses the HIV epidemic, it is believed that an effective HIV response will also support the achievement of other Millennium Development Goals (3)

During the early days, HIV epidemic was delimited to certain specific vulnerable groups of the population with particularly risky behaviors, such as men who have sex with men and injecting drugs users, but it rapidly spread out to general population. Although across the years HIV epidemic became generalized, during last decade, women started to hold an increasing burden of the epidemic, particularly in sub-Saharan Africa(5). Indeed, current

epidemiological estimations point out that in sub-Saharan Africa 60% of all infected individuals are women(6). Paramount of this is that the highest burden of HIV epidemic among women population is hold by girls and younger women (15 – 24 years old), who represent 75% of all HIV-infected women population(6).

Moreover, women of reproductive age are located at the crossroads of HIV transmission, not only participating at HIV sexual transmission through heterosexual intercourses but being the vehicle of the vast majority of pediatric HIV infections through vertical transmission. Although the coverage of effective antiretroviral regimens for preventing mother-to-child transmission has improved in low and middle-income countries, vertical transmission of the virus is still a major threat for the mothers and children who do not access such interventions(7).

In addition, HIV infection is recognized as a leading indirect cause of maternal and child mortality(5, 8). Ensuring a mother living with HIV has access to HIV treatment not only has benefits for her, but also for her family. Studies indicate that children whose mothers stay alive and healthy have a decreased risk of death regardless of the child's HIV status(2). Thus, tackling HIV epidemic among women of reproductive age is recognized as a global health priority. There is now an urgent need for creating updated action plans aiming at eradicating HIV pediatric infections through a more holistic approach, targeting women health and motherhood in its whole spectrum.

Since 2011, global community embraced optimistically the goal of eliminating new HIV pediatric infections by 2015. This goal was established within a global action plan which, besides preventing new HIV pediatric infections, also aims at reducing the excess of maternal mortality due to HIV infection(9). Based on four pronged-strategies, this global action plan aimed at providing the foundation from which national plans will develop, implement and encompass a range of HIV prevention and treatment measures for mothers and their children. These preventive measures are coupled with essential maternal, newborn and child health services as well as family planning as an integral part of countries efforts to achieve Millennium Development Goal 4 and 5(9, 10).

However, more scientific knowledge is needed to correctly deliver this four-pronged strategy. Together with the outstanding improvement of life expectancy owed to ART, a growing desire of childbearing has been documented among HIV-infected individuals. The

reproductive dynamics among HIV-infected women following the initiation of ART are not completely understood and research on these purposes is dearth. Thus, further research is needed in order to propose safe reproductive strategies for HIV-infected individuals willing to procreate.

The research framework of this thesis will firstly introduce the epidemiological and psychosocial context of HIV epidemics among women. The main focus will be done on sub-Saharan Africa and particularly West-Africa, which was the research field of the present work.

Secondly, I'll present a discussion on the subject of vulnerability to acquire HIV infection; focusing in particular on specific vulnerability of sub-Saharan Africa women. This section will be closed with an insight on gender-based violence, specifically intimate partner violence, which was the subject of the first peer-reviewed article I present within this doctoral research framework.

The aim of the second section is to introduce the subject of sexual and reproductive health among HIV-infected women in sub-Saharan Africa. This chapter will start with a brief discussion about current public health challenges in terms of mother-to-child transmission of HIV, to be followed by an insight about sexual and reproductive dynamics among HIV-infected women. The sexual and reproductive dynamics will be presented under an epidemiologic perspective, discussing current trends on fertility intentions among people living with HIV/AIDS, and incidence rates of pregnancy among HIV-infected women on ART. This insight will appear together with a second peer-reviewed article aiming at estimating incidence rates of pregnancy following ART initiation in eight West African countries.

The last chapter of my doctoral framework will focus on repercussion of pregnancy on HIV-infected women's health outcomes. The aim of this chapter is to discuss the repercussion of pregnancy on AIDS disease progression and death among HIV-infected women. One last peer-reviewed scientific article related to former subject will close this chapter.

The present doctoral research framework will be closed with the discussion of my findings and methodology under the perspective of existing scientific evidence. As a conclusion, I'll present my post-doctoral research perspectives.

2. Global background of HIV epidemic

At the end of 20st century, it was estimated that around 34.3 million people were living with HIV/AIDS worldwide(11). Although by this time, HIV epidemic had already reached a global size breadth, the burden of the epidemic varied across the regions worldwide. Roughly 70% of all HIV-infected individuals worldwide were living in sub-Saharan Africa, region holding the highest burden of the epidemic (11). Indeed, rapid spread of HIV pandemic together with its lethal consequences constituted a major menace in terms of global security. In order to roll back HIV pandemic, the global community mobilized an unprecedented amount of human and economic resources.

Ten years later of this outstanding mobilization, the epidemiologic profile of HIV epidemic is less grim. According to current estimations, the number of new infections has significantly declined within a ten years period. In 2012, there were 2.3 (1.9 – 2.7) million of new HIV infections worldwide, representing a decline of 33% of global incidence rate, which was of 3.4 (3.1 – 3.7) million of new infections in 2001(7). Recent estimations show as well that the decline of HIV epidemic was even steeper in 25 low-and-middle income countries where the prevalence rate of HIV infection was of roughly 50% (2). This decline of incidence rate of HIV infection is undoubtedly a result of the great human, economic and political effort deployed worldwide against the pandemic, particularly during last decade towards slowing down the spread of HIV epidemic.

Moreover, the increasing access to antiretroviral treatment has impacted positively life expectancy of HIV-infected individuals, reducing significantly the AIDS-related morbidity and mortality. In 2012, 1.6 (1.4 – 1.9) million people died from AIDS-related causes worldwide compared to 2.3 (2.1 – 2.6) million in 2005(7). Within a seven year period mortality rate of AIDS-related causes declined of roughly 30%(7).This important decline of AIDS-related deaths is owed to the increasing access to life-saving antiretroviral drugs.

The important improvement of life expectancy of HIV-infected individuals owed to antiretroviral therapy together with the relative decline of the number of new HIV-infections, both have provoked a slightly increase of the global HIV-epidemic. In 2012, 35.3 (32.2 – 38.8) million people were living with HIV worldwide compared to the 30.0 (27.2 –

33.1) millions estimated in 2001. However, despite the impressive achievements in rolling back HIV pandemics at a global level, important geographic disparities remain.

2.1. HIV epidemic in sub-Saharan Africa

Within the last decade, several regions have got to reduce importantly the spread of HIV infection, stabilizing their local epidemic. Nevertheless, for sub-Saharan Africa epidemiological trends remained almost unchanged and as shown in figure 1, this region host still the vast majority of HIV-infected individuals (7).

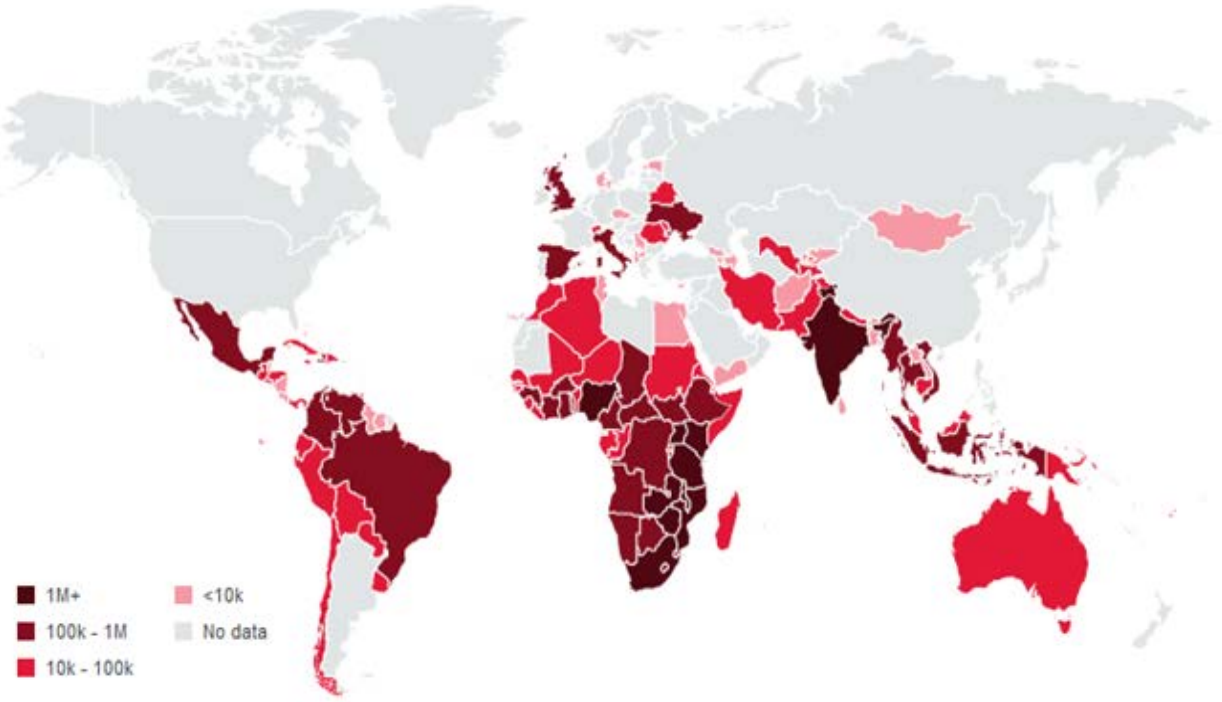

Figure 1. Global distribution of the number of people living with HIV/AIDS.
(Source: AIDS info. 2013: http://www.unaids.org/es/dataanalysis/datatools/aidsinfo/)

According to currents estimations, 70% of the global population infected with HIV lives in sub-Saharan Africa. Indeed, in 2012, 25.0 million [23.5 million – 26.6 million] people are living with HIV/AIDS in this region, among these 2.9 million [2.7 million – 3.3 million] are children (2). Although the number of new infections among adults has observed decline of 34% since 2001; 1.6 million [1.4 million – 1.8 million]of new HIV infections occurred in sub-Saharan Africa in 2012, representing almost three thirds of all new infections worldwide of these year(7, 12).

In addition, although AIDS-related mortality in sub-Saharan Africa decreased of more than half in 2012 (1.2 million AIDS-related deaths; 95%IC: [1.1 million – 1.3 million]) compared to the peak of mortality observed in this region in 2005 (2.1 million AIDS-related deaths; 95%IC:[1.8 million – 2.4 million]), the AIDS-related mortality in this region is higher than any other region worldwide (7, 13). Undoubtedly, the burden of HIV epidemic in sub-Saharan Africa is the highest worldwide

Even though, although HIV infection seems not to discriminate gender or age and, the epidemic is considered generalized, at the beginning of 21st century a particular trend emerged. Owed to specific biologic and context-related factors, the spread of the epidemic started to be more aggressive among women, particularly young women and girls. This particular epidemiologic trend is described in the next chapter.

2.2. Global picture of HIV epidemic during first decade of 21st century: A feminized pandemic

2.2.1. Epidemic overview

According to epidemiologic estimations, in the early days of HIV epidemic, men largely outnumbered women among people living with the virus worldwide(12). However, at the beginning of the present century, epidemiologic trends turned drastically over and HIV infection started to become a real health threat for women, particularly for girls and women of reproductive age.

During early 2000s, prevalence rates of HIV infection were importantly high worldwide and the progress of the pandemic was very aggressive. By this time, besides several countries that were facing epidemics confined to specific risk groups, HIV pandemic was declared generalized (12). However, although epidemic trends pointed out men as the most affected population worldwide, the proportion of females infected by HIV worldwide started to increase steadily(12).

As shown in figure 2, by 2004, of the almost 36 million of adults and children living with HIV/AIDS worldwide, 17 million were women(14). Although the burden of HIV infection was slightly higher among men worldwide; nearly the half of all people infected with HIV between ages of 15 to 49 years old worldwide were women.

Figure 2. Estimated number of adult (age 15 to 49) women (red) and men (black) living with HIV/AIDS by region from 1985 to 2003 (Source: UNAIDS/WHO 2004).

At the beginning of the century, even in high income countries where, the wide availability of antiretroviral treatment and the implementation of effective preventive measures the HIV epidemic was thought to be under control, among adults, the percentage of women living with HIV/AIDS was rising. In North America, 25% of all people living with HIV/AIDS were women; this figure represented an increase of 5% of prevalence rate between 2001 and 2003. Similarly, by this time, in Western Europe epidemiologic estimations pointed out that one out of four HIV-infected individuals was a women(14).

This gender trend of HIV epidemic was even more remarkable in low-and-middle income settings. In Latin America 36% of all HIV-infected individuals were women and this figure was as high as 50% in the Caribbean(14). In South and South-East Asia, women represented more than a quarter of overall HIV-infected adults of this region and 40% of overall young people aged 15 to 24 living with HIV/AIDS (14). Moving more to the West, although somewhat higher, women represented a 33% of all the adult population living with HIV/AIDS in Central Asia and Eastern Europe(14).

The paramount figure of this disastrous gender trend of HIV epidemic was sub-Saharan Africa. In Sub-Saharan Africa, setting reporting the highest epidemic burden worldwide, the progress of HIV epidemic among young girls and women was rampant. In 2004, nearly 60% of all people living with HIV/AIDS in sub-Saharan Africa were women, and 75% of infected individuals between ages of 15 and 24 years old were young women and girls(15). Indeed, HIV epidemic in sub-Saharan Africa, besides being generalized, it was also “feminized”.

As shown in figure 3, since early nineties the number of people living with HIV in sub-Saharan Africa started to be outnumbered by women. By early 2000s, the half of the population living with HIV in sub-Saharan Africa were women (16). In 2002, on average, for every 10 infected men there were 13 HIV-infected women in this region. This proportion was more pronounced in urban areas, with 14 women for every 10 men, than in rural areas, where this relation was of 12 women for every 10 men (14). Alarmingly, this figure was even more pronounced among young people aged 15-24 years old. In South Africa for example among people, for every 10 men aged of 15 to 24 years old infected with HIV there were 20 women of the same age. In Kenya and Mali, this proportion was even worse, for every 10 men there were 45 women(14).

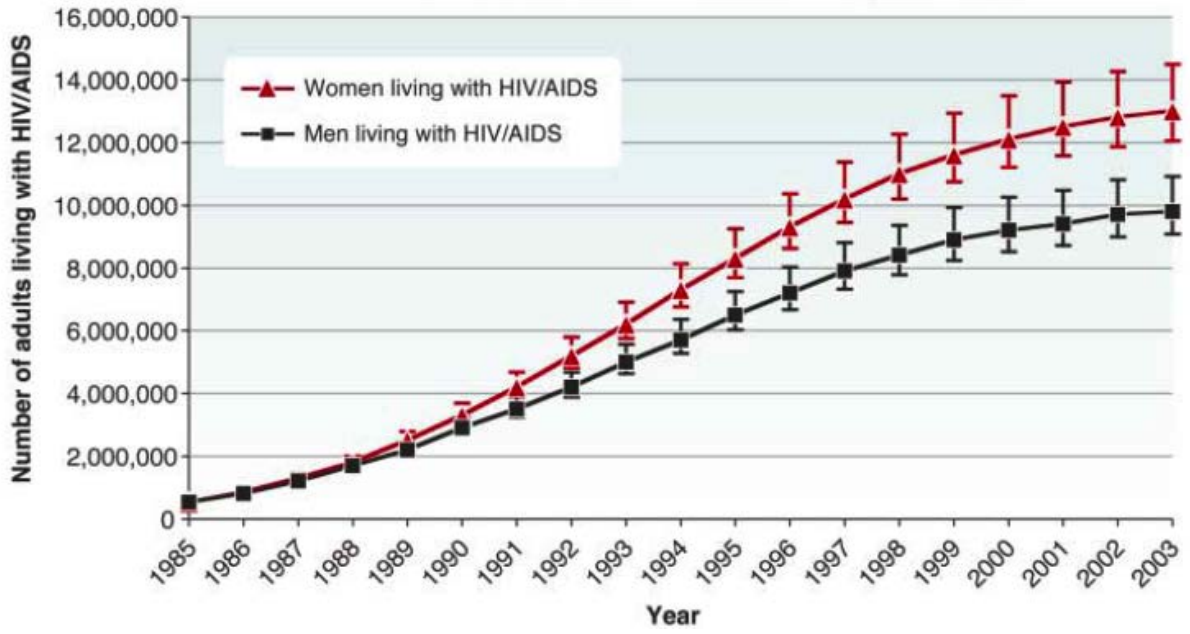

Figure 3. Estimated number of adult (age 15 to 49) women (red) and men (black) living with HIV/AIDS in sub-Saharan Africa over time (1985-2003). (Source: Quinn, T et al, Science 308, 1582 (2005). UNAIDS 2004)

HIV prevalence worldwide was indeed largely outnumbered by women and, this trend was particularly true for sub-Saharan Africa. In this region, women accounted already for more than half of the HIV infected population in certain settings and the risk of acquiring the infection appeared to be outstandingly high among young women. The term *"gender factor"* referring the manifest phenomenon of feminization of the HIV pandemic was used by the first time in 2004 by UNAIDS (14).

Although by the end of the first decade of 21st century HIV epidemic started to reach a relative stability worldwide, this gender trend remained. In 2010, 34 million [31.6 – 35.2] of people were living with HIV/AIDS worldwide and among these 50% were women and girls(17). Sub-Saharan Africa was still the most affected region worldwide with an overall population of people living with HIV of 22.9 million. Women represented 59% of the overall population living with HIV in sub-Saharan Africa(17).

More recent estimations underscored that this gender imbalance was became still more pronounced among young people aged 15 – 24 years old. By 2013, young women make up more than 60% of all young people living with HIV globally and in sub-Saharan Africa this proportion can be as high as 72% (figure 4) (9, 18-20).

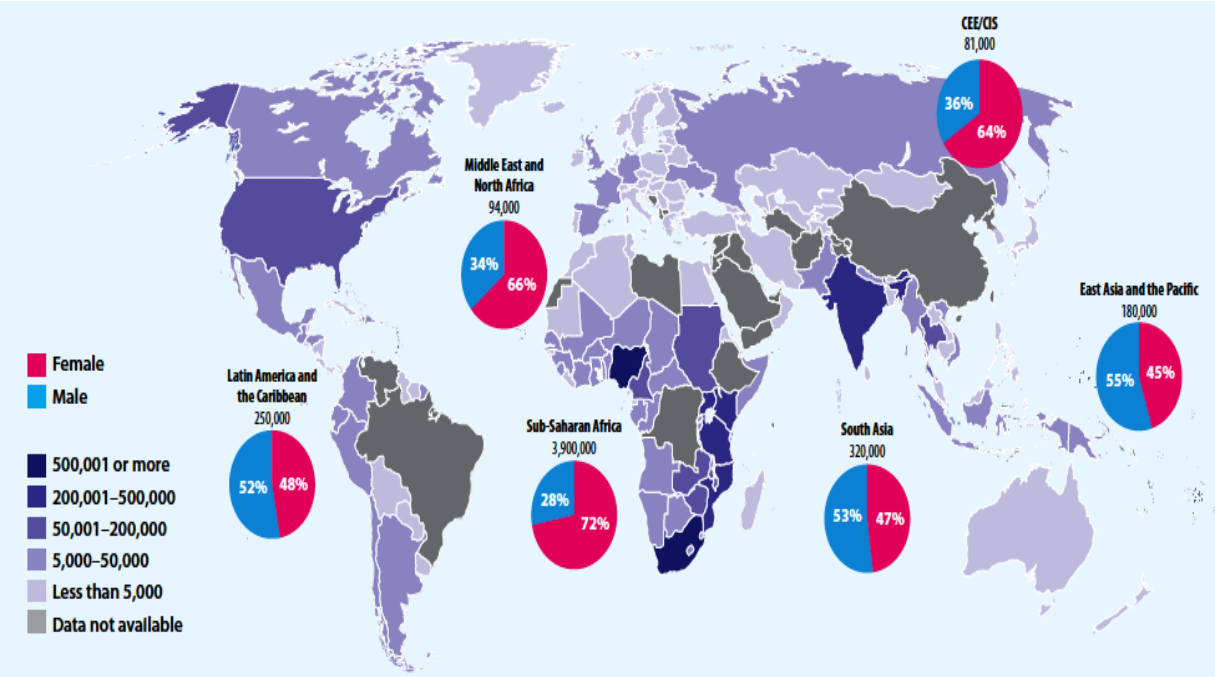

Figure 4. Estimated number of young people aged 15–24 living with HIV, 2009. (Source: UNAIDS/UNICEF 2013).

The risk of acquiring HIV infection among sub-Saharan Africa women was higher than any other group of women worldwide (16). Alarmingly, this risk ratio was strikingly higher among African girls and young women. In several sub-Saharan countries, women aged 15 to 24 years old were three to six times more likely to be infected by HIV than men of the same age group (15, 21).

Even if HIV transmission is a merely biological event, its spread does not occurs necessarily randomly and is profoundly influenced by the surrounding social, economic and political environment(14). It is well known that the higher risk of acquiring HIV infection presented by women resulted of a sum of biological factors and social factors *(explained more in detail in chapter 2)*(12). Biological factors are more related to women's biological constitution but social factors are context-dependent and are more related to the ubiquitous gender disparities prevailing worldwide, particularly in low-and-middle income settings. These gender disparities are distributed at the structural, societal and individual levels (13).

2.2.2. Risk of transmission

Besides the major health risk HIV infection represents for women, there is also the known risk of HIV transmission to their children, carrying therefore important disastrous consequences for the family. The transmission of HIV from an infected mother to her child can occur during pregnancy, labor, delivery or breastfeeding. In the absence of any preventive intervention transmission rates ranges from 15 – 45%(22). This transmission rate can be reduced by 5% with effective biomedical interventions but their limited availability make of mother-to-child transmission an important mechanism fueling HIV epidemic among children (22). Nearly all young children newly infected with HIV are infected through mother-to-child transmission.

In 2005, 470 000 [430 000 – 510 000] children acquired HIV infection from their mothers through vertical mechanisms(22). Although during the last years a great reduction of the mother-to-child transmission rate of HIV has been achieved, an important number of children acquire HIV infection from their mothers. In 2013, 1 260 000 [1 170 000–1 360 000] pregnant women were living with HIV worldwide, transmission rate of HIV from mother to child by this year was of 16% [13 – 18%], estimated number of HIV infected children 200 000 [170 000–230 000] worldwide, from which 89% live in sub-Saharan Africa(22).

2.2.3. Risk of morbidity and mortality

Recent estimations point out that HIV-infection is a source of great morbidity and mortality for women of reproductive age. Tuberculosis, one leading cause of death among HIV infected individuals is highly prevalent among HIV-infected women(23). In 2012, 160 000 HIV-infected women died of tuberculosis, representing 50% of all TB-related deaths among HIV-positive people(23). It is noteworthy that almost 90% of overall HIV-associated tuberculosis deaths among women were in sub-Saharan Africa. Moreover, a positive diagnosis of tuberculosis for a HIV-positive pregnant women is associated with more than double the risk of mother-to-child transmission of HIV to the unborn child and increases the risk of maternal and infant mortality by almost 300%(23).

Currently, HIV-infection has been pointed out as the leading indirect cause of maternal mortality in high prevalence settings. The fraction of maternal deaths attributable to HIV

infection in sub-Saharan Africa is as high as 28% (24). HIV infected women are eight times more likely to die of maternal causes compared to their uninfected counterparts (24).

Finally, according to WHO health statistics, HIV infection is the leading cause of death among women of reproductive age worldwide, responsible of 18.6% of all deaths among this population(25). This proportion of HIV-related deaths among women of reproductive age is as high as 27.9% in low-income settings(25).

To summarize, HIV infection is undoubtedly a major health threat for women, particularly for young women and girls worldwide. Despite the global size of the HIV epidemic among women, the burden of HIV epidemic among sub-Saharan African women and girls appeared to be higher than in any other setting worldwide. The risk of acquiring HIV infection for sub-Saharan African women is higher than anywhere else worldwide. Moreover, the HIV pediatric epidemic is indirectly proportional to the infection rate of HIV among women of reproductive age. Importantly, HIV infection is an important source of morbidity for women of reproductive age and is the leading cause of mortality among this population worldwide.

2.3. Global mobilization towards rolling back HIV epidemic: Actions plans and strategies to roll back HIV epidemic released during 21st century

As at the beginning of 21st century, the burden of HIV epidemic had reached unexpectedly high levels, this creating great awareness within the global community. This great awareness provoked an unprecedented global mobilization of global leaders and stakeholders aiming at designing and implementing public health strategies to roll back the rapid spread of HIV epidemic and provide with clinical care the growing population of people living with HIV/AIDS.

Although by this time the burden of HIV epidemic was already higher among women and girls than any other population group, the inclusion of a gender perspective within global action plans happened progressively. Within the first global action plans, the gender perspective was included probably more as a political statement, articulated transversely within the different preventive and care strategies. It was by the end of the first decade of 21st when global action plans included specific epidemiologic indicators to measure accurately the burden of the epidemic among women and included women-centered preventive and care strategies were included.

The present section outlines the public health frameworks and global strategies to roll back HIV epidemic released within the last decade. These public health frameworks are outlined highlighting the gender perspective included within.

2.3.1. Declaration of commitment on HIV/AIDS (UNGASS 2001)

Alarmed by the outstandingly rapid spread of HIV epidemic worldwide and the magnitude of its disastrous consequences at the beginning of the century, the United Nations General Assembly convened a special session on HIV/AIDS. This high level meeting took place in June 2001 in New York, and was the first-ever United Nations meeting devoted to a public health issue. At this meeting Heads of State and Representatives of Governments of 189 UN members states, issued and signed the Declaration of Commitment on HIV/AIDS (2001)(26).

The Declaration of Commitment on HIV/AIDS (UNGASS 2001) described the extent of the global HIV epidemic at this moment, the effects it has had on human development, and the

way to overcome it. This Declaration stablished time-bound targets and deadlines, which allowed for measurements of government accountability (26).

Within this declaration it was recognized as well that empowering women was one key strategy to reduce vulnerability to HIV infection. It was stated that in order to reduce effectively vulnerability of women and girls face to the epidemic, care and prevention programs must be reinforced including a gender dimension. This gender dimension should advocate for ensuring safe and secure environments, particularly for young women and girls and; expand effective reproductive and sexual health programs.

2.3.2. Three by five strategy

According to UNAIDS and WHO estimations in 2002, 6 millions of people living with HIV were in advanced stages of the disease, urgently needing antiretroviral therapy(12). Out of these 6 million, 4.1 where living in sub-Saharan Africa, where health system were not strong enough to provide clinical care and treatment(12).

Three years later the initiative “three by five” was adopted by the global community and principal objective was to improve the coverage of antiretroviral programs, increasing subsequently the access to antiretroviral treatment(27). This ambitious initiative stablish as target treating 3 million people living with HIV by 2005. The achievement of this goal was based on the following public health approaches:

a. Standardized treatment protocols and simplified clinical monitoring
b. Using existing physical infrastructure and human resources optimally
c. Involving people living with HIV/AIDS as well as communities in designing and implementing programs
d. Simplified record-keeping
e. Minimizing costs of clinical care, including cost of drugs and diagnostics

In order to assure the achievement of this ambitious goal covering with antiretroviral treatment 3 Million people living with HIV within three years, the first global financial mechanism was launched almost simultaneously. The Global Fund to Fight AIDS, Tuberculosis and Malaria was launched by the United Nations in 2002 and its objective was to provide a financial aid to low-and-middle income countries to fight back the three more deadly illnesses by that time: HIV infection, Tuberculosis and Malaria. This global financial

mechanism was funded by industrialized countries and set its secretary office within The United Nations Organization.

In 2003, one year after the United Nations Organization launched the Global Fund, the government of the United States under the mandate of President George W. Bush, launched the President's Emergency Plan for AIDS Relief (PEPFAR). Committed to fight the global AIDS pandemic, this initiative aimed initially to increase antiretroviral treatment and clinical care coverage in sub-Saharan Africa.

2.3.3. Three ones strategy

Subsequently and in order to propose a strategy to track the targets stablished within The Political Declaration of UNGASS 2001, a guiding framework was proposed by global community. The three ones principles was a strategy recognized by international organizations and national governments as the guiding principles to ensure effective coordination of national responses to HIV/AIDS(28).

The three ones principles were endorsed in 2004 in Washington D.C. by UNAIDS major bilateral donors, UNAIDS cosponsors, other key international organizations and national governments. These principles challenged the growing number of strategies, committees and monitoring systems, which were adding confusion, increasing transaction costs for countries and detract from impact(29).

The rationale behind the formulation of these three guidance principles was to ensure a harmonized, coordinated and country-owned response to HIV epidemic. Thus, aiming at reinforcing the commitment of international stakeholders to coordinate contributions to the HIV epidemic at the national level, the following principles were stablished(29):

One agreed HIV/AIDS Action Framework that provides the basis for coordinating the work of all partners;

One National HIV/AIDS Coordinating Authority, with a broad-based multi-sectorial mandate;

One agreed HIV/AIDS country-level Monitoring and Evaluation (M&E) System.

Later on, in 2005, leaders of the G8 countries agreed to work with WHO, UNAIDS and other international bodies to develop and implement wide scaled efforts to overcome HIV

epidemic globally, with the aim to achieve universal access to treatment combined with prevention and care, for all those who need it by 2010. This goal was subsequently endorsed by all United Nations Members States at the 2005 UN Millennium Summit, high level meeting gathering the largest number of world leaders in history(30).

The values and principles of the political declaration yielded of the 2005 UN Millennium Summit reaffirmed that in order to advance development and roll back HIV epidemic, it was essential to promote the gender equality and protect human rights and fundamental freedom for all, in particular for women and girls (30).

On the light of formers agreements and taking into account the significant progress rolling back HIV epidemic, within The General Assembly High Level Meeting of HIV/AIDS of 2006 global community decided to assume more ambitious targets to control HIV epidemic spread. In 2006, the United Nations Member States agreed to work towards a broader goal of "*Universal Access to comprehensive prevention programs, treatment, care and support*" by 2010 to all those in need. This broader goal was stablished within the Political Declaration on HIV/AIDS of 2006(31).

2.3.4. Zero strategy

In 2010, the "Getting to Zero" strategy was launched by UNAIDS in partnership with other United Nations agencies and private and public sector partners. This strategy aimed at accelerating and advancing global progress in achieving country set targets for universal access to prevention, treatment, care and support, halting and reverting the spread of HIV epidemic, and contributing the achievement of the Millennium Development goals by 2015 (32). The strategy was supported by three main visions, resuming the principles goals stablished to roll back HIV epidemic by 2015:

1. Zero new HIV infections
2. Zero AIDS-related deaths
3. Zero discrimination

It is worth to note that, The Getting to Zero strategy was probably amongst the first strategies encompassing the gender dimension within their global approach with gender-specific and measurable targets(32). Amongst the goals of the third strategic direction of this strategy it was set out that national responses to HIV of countries committed, must address

comprehensively the HIV-specific needs of women and girls and advocate for a zero tolerance for gender-based violence, recognized as a major driver of women-specific vulnerability to acquire the infection(32).

These gender-specific goals emerged from the fact that although a growing number of women were becoming infected, the most of the funding allocated to women issues was only destined to provide antiretroviral therapy to prevent mother-to-child transmission(32). As in most affected regions women represented 60% of all the population living with HIV/AIDS, it was essential to combine HIV related funding with other resources to address the full range of women's vulnerability such programs for serodiscordant couples, young women and female sex workers and particularly to foster the change of the harmful gender norms and economic disempowerment(32).

The "Getting to Zero" strategy was probably the strategy setting the pace towards a real comprehensive approach of HIV epidemic with a gender-specific approach, outlining clear and measurable goals to tackle HIV epidemic among women and girls.

2.3.5. The Political Declaration on HIV/AIDS of 2011

In 2011, thirty years since the first case of AIDS was identified, ten years since the landmark United Nations General Assembly Special Session on HIV/AIDS took place and five years since the 2006 High Level Meeting, where the "Universal Access commitment" was made, the global agenda moved towards a more sustained scale-up of national responses to HIV/AIDS. The Political Declaration on HIV/AIDS of 2011 claimed to an intensification of the efforts to eliminate HIV/AIDS(33). This political declaration was unanimously adopted by UN member states and the commitment was to redouble efforts to achieve a set of ten more ambitious goals by 2015. In alignment with the Millennium Development Goal 6: Combat HIV/AIDS, the targets stablished in 2011 were clear:

1. Reduce sexual transmission of HIV by 50%
2. Halve the transmission of HIV among people who inject drugs
3. Eliminate HIV infections among children and reduce maternal deaths
4. Reach 15 million people living with HIV with lifesaving antiretroviral treatment
5. Halve tuberculosis deaths among people living with HIV
6. Close the global AIDS resource gap

7. Eliminate gender inequalities and gender-based abuse and violence and increase the capacity of women and girls to protect themselves from HIV
8. Eliminate HIV-related stigma, discrimination, punitive laws and practices
9. Eliminate HIV-related restrictions on entry, stay and residence
10. Strengthen HIV integration

In addition, the UN member states attending to this high level meeting pledged also to close global resource gap for overcoming the HIV epidemic and work towards increasing funding to expand global and national responses to HIV/AIDS. It was recognized as well that the investment into the HIV response is a shared responsibility which demands a sustained cooperation of global community together with an in-country investment.

Finally, it was recognized as well that to narrow the funding gap and meet funding needs, designing strategic investment plans was compulsory. These strategic investments plans must foster the creation and sourcing of innovative financing mechanisms increase the national ownership of HIV responses and assure that funding is aligned to national responses priorities and strategies.

In summary, we observed over the last decade a positive evolution of the political commitment aiming at rolling back the HIV epidemic, progressively coupled with specific targets to tackle the spread of HIV epidemic among women and girls. This positive evolution of political commitment is evidenced by the inclusion of gender specific axes within the new generation of global action plans to tackle HIV epidemic, aligning policies, strategies and public health actions to scale-up HIV prevention and care programs through a gender equitable perspective.

3. Scaling-up the access to HIV care: towards the universal access to antiretroviral therapy in constrained-resources settings

3.1. Contextualization

Since introduction of antiretroviral drugs the life expectancy and the quality of life of people living with HIV/AIDS has dramatically improved. The great effort deployed to make available these drugs worldwide has been a cornerstone to reduce the burden of HIV epidemic and to slow down it rapid spread. In 2011, by the time United Nations released the political declaration claiming for an intensification of the efforts to eliminate HIV/AIDS, the access to antiretroviral therapy had already increased of 63% since 2009 worldwide. In low-and-middle income countries 54% of HIV-infected individuals needing antiretroviral therapy were receiving it. Overall, 8 million people living with HIV/AIDS were accessing to antiretroviral therapy worldwide in 2011, being 2 million more than in 2009(34).

This progressive increase of the percentage of people living with HIV/AIDS acceding to antiretroviral treatment was traduced in more than half a million fewer deaths in 2011 than in 2005 worldwide(34). Only in sub-Saharan Africa, the increasing availability of these drugs reduced by 32% the number of AIDS-related deaths between 2005 and 2011(34).

In addition, the incidence rate of tuberculosis among HIV-infected individuals, the most deadly HIV comorbidity, has reduced importantly since the increasing availability of antiretroviral drugs. Indeed, TB-related deaths fell by 25% worldwide and 28% in sub-Saharan Africa(34).

Besides the well-known benefits of combination antiretroviral therapy on decreasing viral replication and improving the survival of HIV-infected persons, it has also an important preventive effect. Evidences of the potential preventive benefit of antiretroviral therapy are available since mid-nineties, when it was clinically demonstrated that the administration of short courses of antiretroviral drugs during pregnancy and breastfeeding reduce significantly the risk of mother-to-child transmission of HIV. This biomedical intervention was among the first showing a significant preventive.

Furthermore, biomedical research explored the potential benefits of antiretroviral treatment in preventing sexual transmission of HIV. The preventive power of antiretroviral treatment was explored among uninfected individuals before and after a risk exposure to HIV infection.

Findings from recent studies such as *iPREX* and *CAPRISA 004* confirmed the effectiveness of preexposure antiretroviral prophylaxis (PrEP) on preventing sexual transmission of HIV (35-38). Emergency ART, the best example of post-exposure prophylaxis, is considered the standard of care after occupational exposures to HIV. Although a growing number of countries started to offer antiretroviral therapy in cases of non-occupational exposures, it was more an empirical practice, its efficacy was not proven by a clinical trial (39). However, as former biomedical interventions are addressed to uninfected individuals and their aim is to reduce the risk of contracting HIV infection through a risk contact, their implementation is limited by ethic and economic issues.

Thus, within this context, a novel preventive hypothesis emerged setting out that if HIV transmission is only possible through the contact with biological fluids (blood, genital fluids and breast milk) of HIV-infected individuals containing active virus then, a sustained viral suppression within these fluids may reduce the risk of HIV transmission, leading to a significant decline of new HIV-infections. This hypothesis drove the new HIV preventive approach of *"Treatment as Prevention"* (TaSP).

Mathematical models aiming at quantifying the virtual preventive benefit of the systematic initiation of antiretroviral treatment following a HIV-positive test regardless clinical status, pointed out that theoretical positive impact of these strategy on reducing the number of new HIV-infections (40). In 2011, the multicountry randomized control trial HPTN 052 aiming at evaluating the effect of combination antiretroviral therapy on the prevention of HIV-1 transmission among serodiscordant couples confirmed that, besides the recognized benefits of antiretroviral treatment on improving health status of HIV-infected individuals, it is also a powerful HIV preventive strategy *(see box 1)*(41).

In summary, antiretroviral therapy, besides increasing importantly the life expectancy and quality of life of people living with HIV/AIDS, has a powerful demonstrated preventive effect, reducing significantly the number of new HIV infections among adults and children. Thus, in order to achieve the ambitious goals set out by the United Nations Declaration of 2011, a massive scale-up of HIV treatment, was indeed a key public health strategy. In line with these global goals, the actions to achieve this massive scale-up of HIV-treatment were encompassed within global action plans.

BOX 1. Benefits of an early initiation of antiretroviral therapy: ART as a preventive strategy

The potential benefit of antiretroviral therapy in preventing sexual transmission of HIV has been object of scientific research during last years. Mathematical modeling showed that universal voluntary HIV testing once a year of all people older than 15 years, combined with immediate ART after diagnosis, could bring about a phase change in the nature of the epidemic. These model suggests that massive scale-up of universal voluntary testing with immediate initiation of ART could nearly stop transmission and drive HIV into an elimination phase in high-burden setting with 1-2 years of reaching 90% of program coverage (Granich et al. Lancet, 2009).

In 2011, Cohen et al conducted a randomized control trial among 1763 serodiscordant couples aiming at evaluating the impact of at enrollment initiation of antiretroviral treatment –regardless clinical status -, on HIV-1 sexual transmission and on clinical events in infected persons versus a delayed initiation. Findings of this study showed, that besides the outstanding restoration of clinical status, an early initiation of antiretroviral treatment provides real benefits on preventing HIV sexual transmission. The risk of transmission of HIV-1 observed a relative reduction of 96% among early ART starters, as compared with delayed therapy.

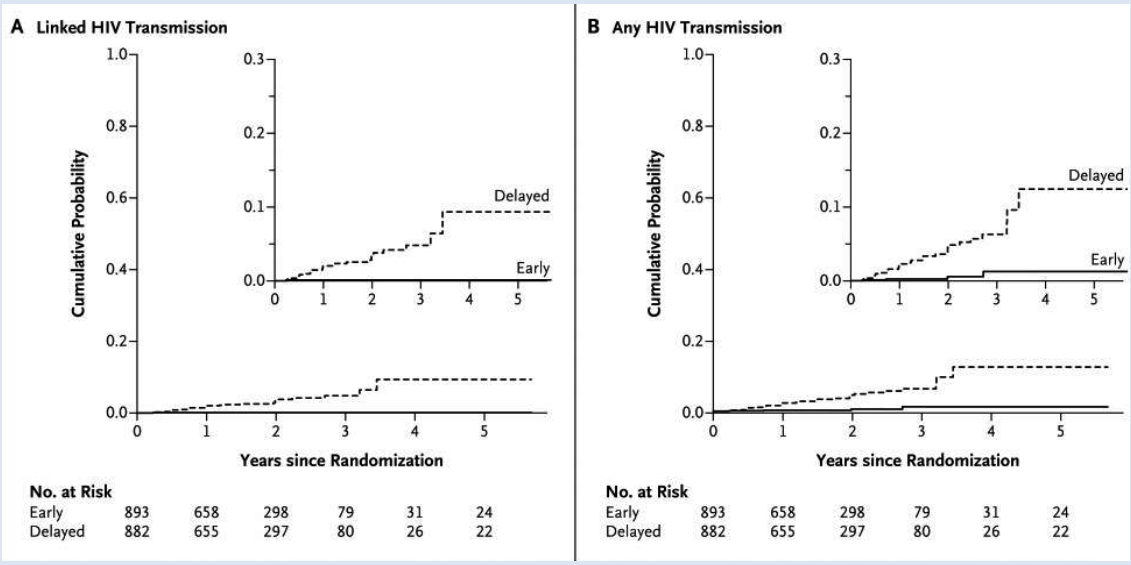

Figure 5. Kaplan–Meier Estimates for Partner-Linked and Any HIV-1 Transmission. Cohen et al, 2011

On the light of these promising results, investing in expanding ART coverage might have an outstanding public health impact. Indeed, besides the acknowledged benefits of ART on reducing morbidity and mortality of HIV-infected individuals, it does have the power to reduce the number of new infections.

***Reference**: Cohen, M. S., Y. Q. Chen, et al. (2011). "Prevention of HIV-1 infection with early antiretroviral therapy." N Engl J Med 365(6): 493-505.*

3.2. Global action plan: “Treatment 2015”

According to UNAIDS estimations, 6.6 million people in low- and middle-income countries were receiving treatment at the end of 2010 of the estimated 14.2 million people eligible, nearly the half (47%) of all the people in need of these drugs were receiving it(42). Under the light of these estimations, achieving the global target of reaching 15 million people with antiretroviral treatment was indeed a major challenge for global community; therefore an action plan was required to organize a global response.

In 2013, UNAIDS joined with WHO, the US President’s Emergency Plan For AIDS Relief (PEPFAR), the Global Fund to Fight AIDS, tuberculosis and Malaria and other partners to launch the “Treatment 2015” initiative. “Treatment 2015”, is a global action plan which emphasizes speed in scaling up, enhanced strategic focus to intensify scale-up in key geographic areas and populations, and innovation in program planning and service delivery(7, 43). This global action plan set out a particular focus on women, advocating for gender equality in terms of access to care (7, 43).

3.3. Rationale of global action plan: Treatment 2015

Accelerating the scale up of antiretroviral therapy will drive progress across the broader AIDS response. It will reduce HIV-related illness and death, prevent people from acquiring HIV infection, address the needs of women and girls, reduce stigma and social exclusion and promote service integration(43).

However, the eligibility to receive these drugs is determined by a combination of clinical and biological criteria. In order to establish standard criteria of ART-eligibility, the World Health Organization (WHO) has been collecting, evaluating and systematizing scientific evidence since the advent of antiretroviral treatment in resource-limited settings. These criteria are fundamentally based on CD4 cells measurements.

According to WHO guidelines of 2010, all HIV individuals having <350 CD4 cell/mm3 were recommended to start antiretroviral treatment(44). Under this criterion, it was estimated that 61% (57% - 66%) of all persons eligible for HIV treatment in low-and-middle-income countries had obtained antiretroviral therapy in 2012(7). In settings, where the coverage with Antiretroviral treatment has reached levels over 80% under the 2010 WHO treatment

guidelines (initiate treatment at a CD4 cell count of 350 cells/mm3 , incidence of HIV-infection has observed an important reduction (44, 45).

The positive effect of the introduction of ART on averting new HIV infections is practically undeniable. In 2013, WHO guidelines on antiretroviral treatment were updated and the biological threshold established to initiate treatment changed. According to this last update of WHO guidelines treatment was recommended for all individuals having between >350 CD4 cells/mm3 and <500 CD4 cells/mm3 regardless their clinical stage (46).

Achieving and maintaining 80% global coverage under the 2013 guidelines would prevent more than 3 million additional AIDS related deaths and prevent an additional 3.5 million people from acquiring HIV infection through 2025, in comparison with the 2010 guidelines(43, 45, 46). Higher reductions of new infections are expected with the full implementation of new WHO treatment guidelines released on 2013 (initiate antiretroviral treatment at 500 CD4 cells/mm3)(46).

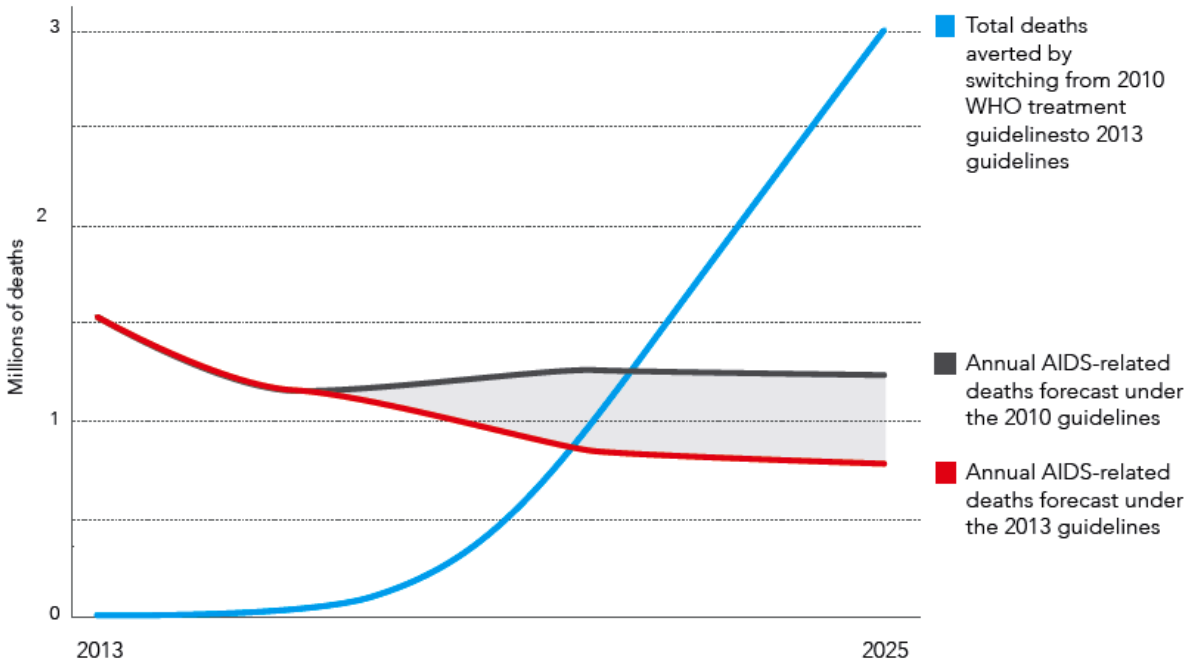

Figure 6. Impact of implementation of 2013 WHO guidelines of antiretroviral treatment use in terms of number of AIDS-related deaths averted. (Source: UNAIDS, 2011).

Besides de important benefits of antiretroviral treatment increasing life expectancy and improving quality of life of HIV infected individuals, may contribute importantly with economic development of the most severely affected countries. Scaling up antiretroviral

therapy fosters future economic growth, strengthening and preserving the health and well-being of adolescents and young adults which are the most important work force.

3.4. Current status of universal access to antiretroviral treatment: 15 Million by 2015

At the time the global action plan "Treatment 2015" was launched in 2012 around 9.7 million people living with HIV/AIDS were accessing to antiretroviral treatment in low-and-middle-income countries(42, 43). Under WHO guidelines of 2010, 61% of all HIV-infected individuals eligible for antiretroviral treatment where accessing to these live saving drugs and 34% under WHO guidelines of 2013(34).

According to currents global estimations, the number of people living with HIV receiving antiretroviral treatment observed an important increase. In 2013, 12.9 million HIV-infected individuals were accessing to treatment meaning an increase of 3.2 million individuals within one year(34). These estimations seem to be optimistic as the proportion of people living with HIV covered by antiretroviral programs represents 86% of 15 million targeted.

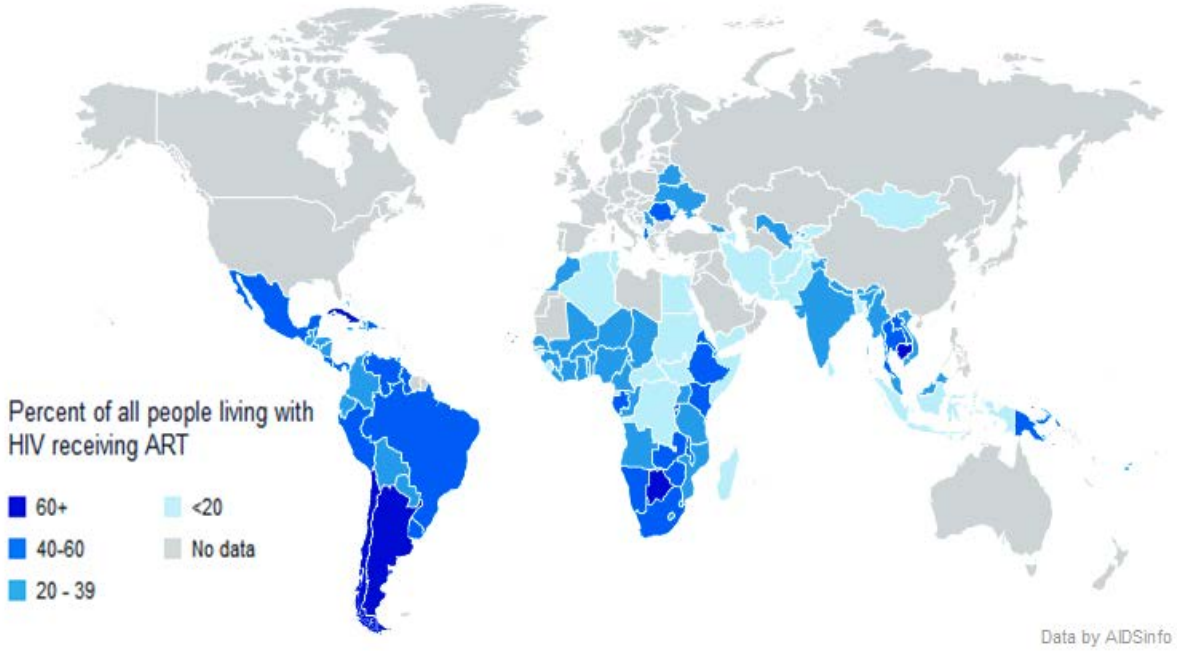

Figure 7. Percentage of all people living with HIV receiving ART worldwide. (Source: UNAIDS/AIDS info)

In sub-Saharan Africa, setting with highest prevalence rates of HIV-infection, increasing coverage of antiretroviral programs is a major public health challenge. Although currents trends are somewhat encouraging, important gaps in terms of access to antiretroviral therapy persist in sub-Saharan Africa. The breadth of these gaps is changeable and as shown

in figure 7, the percentage of people living with HIV/AIDS receiving antiretroviral drugs varies importantly worldwide. The proportion of adults living with HIV/AIDS eligible for and receiving antiretroviral treatment in sub-Saharan Africa is amongst the lowest worldwide.

Indeed, in at least 14 countries at the south of the Sahara, 80% or more of people who were estimated to be eligible for treatment under the 2013 WHO guidelines were not receiving antiretroviral therapy at the end of 2012(47). Additionally, this gap appeared to be deeper in Western and Central Africa where only around 20% of all HIV-infected people eligible for antiretroviral treatment are currently receiving it (47).

In southern and eastern Africa, although coverage appeared to be higher this gap represents around 40% of HIV-infected people eligible for antiretroviral treatment who have not yet started(47). Currently, antiretroviral programs of an important number of sub-Saharan countries have barely achieved a 40% of coverage (20% – 39%). Given that women constitute more than half of the population living with HIV in sub-Saharan Africa, the expected massive increase of the coverage of antiretroviral programs will be undoubtedly outnumbered by women.

4. Mother to child transmission of HIV

By 2010 an estimated 390 000 [340 000–450 000] children became newly infected with HIV worldwide (42). The vast majority of these children acquired the infection from their mothers during pregnancy or postpartum through breastfeeding. This number represents an important drop of new HIV pediatric infections from 2002, year where pediatric infections reached a peak of 560 000 (340 000 – 450 000)(42). For most of high income countries, the elimination of new HIV pediatric infections is practically a reality. In United States for example the proportion of new HIV infections among children fell by 93% within a ten years period (1992 – 2005)(48). Despite this important drop of the number of newly HIV-infected children, the target of elimination of new HIV pediatric infections faces still important public health challenges.

For a growing number of resource-limited settings, the elimination of new HIV pediatric infections is not anymore utopic. By 2011, the prevention of mother-to-child transmission programs of several low-and-middle income countries started achieving 80% of coverage(42). Botswana was an outstanding example, were the percentage of infants who are born HIV-positive to mothers living with the virus declined from 21% in 2003 to 4% in 2010(42). Likewise, several other southern and eastern Africa countries have successfully achieved universal access to prevent new HIV pediatric infections(42). Indeed, the goal of taking to zero new HIV pediatric infections was almost a reality for an important number of countries.

However, the pediatric epidemic was principally concentrated within 22 countries which were hosting 90% of all pregnant women living with HIV and in need of clinical care in 2012 (42). Among these 22 countries, besides India, all were located in sub-Saharan Africa: Angola, Botswana, Burundi, Cameroon, Chad, Côte, d'Ivoire, Democratic Republic of the Congo, Ethiopia, Ghana, India, Kenya, Lesotho, Malawi, Mozambique, Namibia, Nigeria, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia and Zimbabwe(42).

4.1. Coverage of HIV testing services for pregnant women.

In 2009, the proportion of pregnant women in low-and-middle income countries who received an HIV test was as low as 26%(6). The limited integration of HIV services within antenatal care services is major barrier to the early detection of HIV-infected pregnant women and therefore a primary limitation to implement preventive strategies during pregnancy. Offering an HIV test and counseling was not systematic within antenatal services and in consequence, the initiation of prophylactic treatment was delayed, increasing therefore the risk of HIV transmission.

In 2009, 53% of all HIV-infected pregnant women in low-and-middle income countries received antiretroviral medication to prevent mother-to-child transmission of HIV during pregnancy and/or postpartum(6). Moreover, for those HIV-infected mothers accessing preventive antiretroviral strategies, the distribution of antiretroviral regimens varied importantly, particularly among the 22 prioritized countries. Although trends were shifting, the overall proportion of HIV-infected mother who were receiving a three-drug regimen was less than 10% (figure 8). The benefits of a global shifting to a three-drugs regimens would provoke an immediate drop in the number of new HIV infections among children(42)

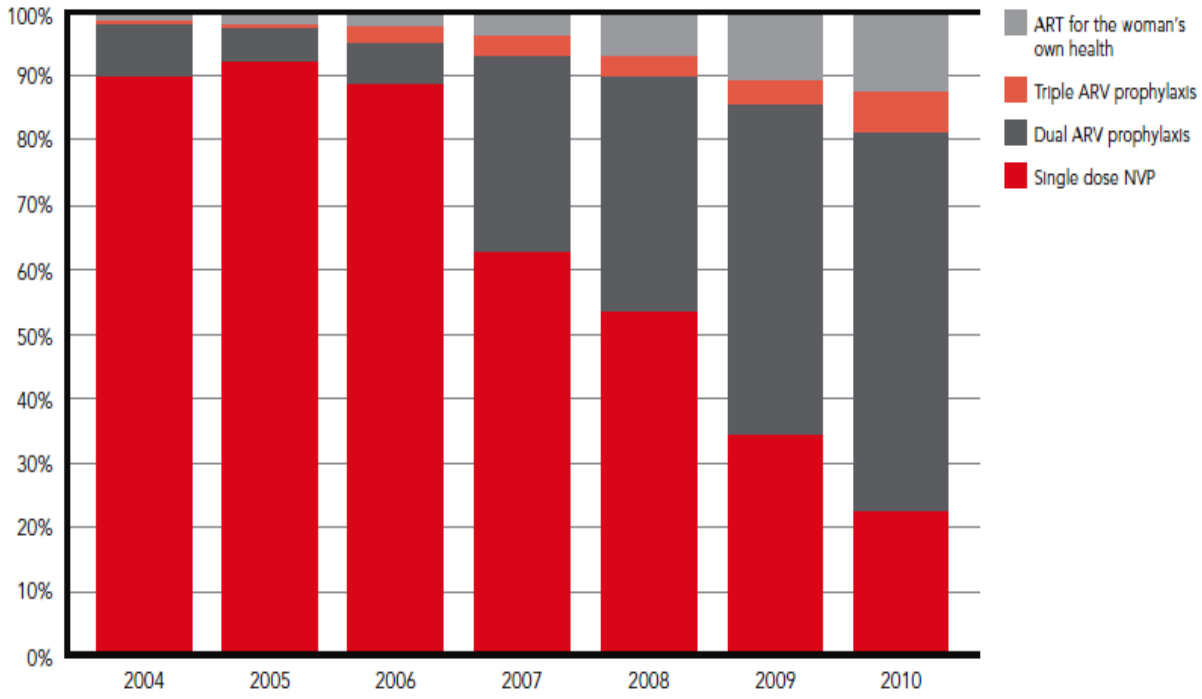

Figure 8. Distribution of antiretroviral regimens to prevent new HIV infections among children: 22 priority countries, 2004–2010

These former structural and operational obstacles, together with the high epidemic burden held by women of reproductive age and the large access gap to family planning estimated in these settings, constituted major menaces to the achieve the full elimination of new HIV pediatric infections. As a consequence, an updated global action plan encompassing effective evidence-based strategies targeting these obstacles was urgently needed.

4.2. Global plan towards elimination of new HIV infections among children by 2015 and keeping their mothers alive

4.2.1. Concept and rationale of the global action plan

In 2011, the global community embraced a new challenging goal aiming at eliminating new HIV infections among children and reducing AIDS-maternal deaths by 2015. This ambitious goal was included within the Global Action Plan Towards Elimination of New HIV Infections among Children by 2015 and Keeping their Mothers Alive launched in 2011 by UNAIDS (9).

This global action plan lies on a more comprehensive public health approach targeting women, maternal and child health in it whole spectrum. On the one hand, the public health strategy proposed by this plan aims at reducing the incidence of HIV infection among women of reproductive age and preventing unintended pregnancies, narrowing the gap of unmet needs for family planning. On the other hand, this strategy aims at increasing the coverage of preventive programs and providing women with ART to reduce AIDS-related morbidity and mortality and prevent the vertical transmission of HIV. Although this global action plan is addressed to all resource-limited settings, the 22 countries holding the highest prevalence rates of HIV among pregnant women are the priority(9).

The goals of this action plan are consistent with the current global development priorities. The framework of this global action plan is in alignment with four of the Millennium Development Goals (MDG), where HIV is holding back progress. Firstly, preventing new HIV infections among women of reproductive age, fostering the access to HIV prevention and treatment services, delivering sexual and reproductive health services and involving HIV-positive mothers as key partners to deliver this plan contributes directly with MDG 3, which claims for gender equality and women empowerment.

Secondly, as HIV is considered a major cause of maternal and child mortality, providing them with appropriate health care services and treatment to prevent new HIV pediatric infections and to treat those mothers and children already infected have undoubtedly a positive impact in the progress of MDG4 and MDG5, aiming at the reduction of child mortality and improving maternal health respectively(49).

Finally and very importantly, this global plan contributes outstandingly with the achievement of MDG6, combating HIV/AIDS, preventing its spread among women of reproductive age and children, providing treatment and care for mother living with HIV/AIDS and reducing AIDS-related morbidity and mortality among this population.

4.2.2. Configuration of the global action plan

As shown in figure 9, this global action plan is constituted by two global targets which are expected to be achieved through a four-pronged strategy.

Figure 9. Configuration of the Global Plan of Elimination of New HIV Infections among Children and keeping their mothers alive (source: UNAIDS 2011).

In order to assess the progress towards the global goal of this action plan, each prong includes a comprehensive package of items to be tracked.

1. **Global target 1:** Reducing by 90% all new pediatric infections/ Reduce AIDS-related infant deaths by >50%.

Three prongs are designated to measure the achievement of this goal. Preventing new HIV pediatric infections in primary based on reducing the spread of HIV infection among women of reproductive age (*prong 1*) and preventing unintended pregnancies (*prong 2*). Together with the third prong which aims at actively preventing HIV transmission through the provision of appropriate care and treatment to pregnant women living with HIV, these three first prongs are expected to reduce new HIV pediatric infections to the expected levels.

2. **Global target 2:** reduce by 50% the number of AIDS-related maternal deaths

As a part of the public health approach, to measure this goal, the indicator will capture a broader package of HIV and maternal, newborn and child health services (prong 4). This global action plan presents an unprecedented opportunity to tackle Millennium development objectives 5 and 6 specifically(50). In addition, this target is in line with the goals set out in the Countdown to 2015 initiative for maternal, newborn and child survival(49).

Besides preserving mother's lives is a legitimate action on its own; the impact of keeping children alive and free of HIV infection will be limited if their mothers are no longer there to take care of them. The indicator is the number of HIV-related deaths among women who were either pregnant or gave birth in the preceding six weeks.

4.2.3. When to start ART during pregnancy

ARV drugs are used for pregnant and breastfeeding women infected with HIV primarily for the mother's health and to prevent the exposed child from becoming infected. Besides these health benefits, it may also offer benefits on preventing the sexual transmission of HIV.

Concerning the therapeutic management of pregnant women living with HIV and their children, this action plan is in line with the updated WHO guidelines about prophylactic ART regimes released in 2013. The preventive strategy proposed by the global plan of elimination

is based on a triple antiretroviral therapy for all HIV-infected pregnant women regardless their clinical status.

Before 2010, recommended prophylactic regimens during pregnancy and postpartum were based on short-course of antiretrovirals, starting during pregnancy and continued until several weeks of postpartum. From 2010, WHO PMTCT guidelines stated that lifelong ART was only recommended for pregnant women living with HIV meeting eligibility criteria for treatment (based on the 2010 eligibility criteria of CD4 counts ≤350 cells/mm3 or presence of WHO clinical stage 3 or 4 disease) (44). For HIV-infected pregnant women not meeting treatment eligibility criteria, two prophylactic strategies were recommended:

1. **Option A**, AZT for the mother during pregnancy, single-dose NVP (sd-NVP) plus AZT and 3TC for the mother at delivery and continued for a week postpartum; this was coupled with daily NVP given to the infant throughout breastfeeding exposure(44)
2. **Option B**, triple ARV drugs for the mother during pregnancy and throughout breastfeeding. Prophylaxis was recommended to start as early as 14 weeks of gestation, and both prophylaxis options included four to six weeks of peripartum NVP or AZT for the infant, regardless of whether the mother was breastfeeding(44).

Although these two prophylactic regimens do offer a benefit in terms of preventing HIV transmission from the HIV-infected mother to her child, several operational barriers limited their optimal efficacy. Although available data continue to show that the *Option A* and *Option B* prophylactic regimens have similar efficacy in clinical trial context, the complexities of Option A have been an impediment to scaling up PMTCT in many countries(46). These complexities include different treatment and prophylactic regimens; the requirement for CD4 cells measurement to determine treatment eligibility and type of regimen; changing antepartum intrapartum postpartum regimens; the need for an additional postpartum ARV "tail" in mothers; and extended NVP prophylaxis in infants.

In order to achieve the global goal of elimination of new HIV infections among children, WHO guidelines about prophylactic therapies to be used during pregnancy and postpartum evolved. In 2011, Malawi implemented a new approach of lifelong ART for all pregnant and breastfeeding women with HIV regardless of CD4 count or clinical stage, commonly referred to as "*Option B+*"(51). WHO issued a programmatic update in April 2012, outlining some of the operational advantages of *Option B* and the emerging strategy of *Option B+*(52).

In 2013, for programmatic and operational reasons, *Option A* was no longer recommended and current WHO guidelines recommend that all pregnant and breastfeeding women with HIV should initiate triple ARV during the period of risk of mother-to-child transmission and continue lifelong antiretroviral treatment, regardless CD4 count or clinical stage(46). Although the recommendation of *Option B+* is based on moderate-quality scientific evidence, it was suggested to offer an important number of operational benefits**.**

Public health benefits of Option B+:

1. Covering pregnant women living with HIV with antiretroviral therapy reduce significantly AIDS-related maternal mortality.
2. As an important number of pregnant women report to be in a stable couple, ART initiation offers protection from HIV transmission.
3. ART initiation will protect current and future children against the acquisition of HIV infection from their HIV-infected mother through vertical mechanisms.

In addition, Option B+ provides as well structural benefits for health systems. The same simplified ARV regimen administered to all pregnant women (regardless of clinical eligibility) and continued during pregnancy and labor and postpartum is easy to deliver. The optimized first-line fixed-dose combination regimen can be harmonized with guidelines for ART in non-pregnant adults. Finally, Option B+ ensures that immunocompromised women who do not have access to CD4 testing receive appropriate ART without delay.

To accelerate the rapid global scaling up of ART and PMTCT in resource-limited settings, ensure equitable access to ART for pregnant women and achieve the global goal of eliminating new pediatric infections and keeping mothers alive, recommendations now need to be further simplified, standardized and harmonized however.

4.2.4. Progress status of global plan implementation

Current estimations show that the implementation of the global action plan of elimination of new HIV infections among children and keeping their mothers alive started to yield encouraging but entirely satisfactory results. According to estimations of UNAIDS, 240 000 (210 000 – 280 000) children became newly infected worldwide in 2013, down from 580 000 (530 000 – 640 000) in 2001, this represents an impressive decline of 58%(34).

This important reduction of new HIV pediatrics infections has been partly owed to the great progress observed by the programs for prevention of mother to child transmission. The coverage of such programs (excluding the less effective sd-Nevirapine regimen) increased from 57% (51 – 64%) in 2011 to 62% (57 – 70%) in 2012(7). Owed to this modest increased coverage rate, more than 670 000 new HIV pediatric infections were prevented between 2009 and 2012.

In 2013, two years after this global action plan was launched, great achievements have been documented among the 22 prioritized countries. Among prioritized countries at least seven high-burden countries reduced by 50% the estimated number of new pediatric HIV infections from 2009 levels (Botswana, Ethiopia, Ghana, Malawi, Namibia, Zambia and Zimbabwe) and four more (Mozambique, South Africa, Uganda and the United Republic of Tanzania) fall out very short to achieve this goal(19). Moreover, the transition from the use of sd-Nevirapine as primary antiretroviral preventive option for pregnant women living with HIV, to more effective antiretroviral regimens is a real for all priority countries(19).

BOX 2. Scaling-up of mother-to-child transmission of HIV prevention programs: Malawi and the successful story of the Option B+

According to 2010 WHO guidelines, for pregnant women living with HIV, the eligibility for a lifelong antiretroviral treatment or a short-course preventive antiretroviral regimen depended on biological and clinical criteria. To determine this eligibility to one or another regimen all pregnant women must realize at least one CD4 cell count.

In 2011, in Malawi, East-African country with a generalized HIV epidemic was facing an important challenge scaling up their in-country mother-to-child transmission of HIV prevention program. The limited local capacity to carry out CD4 cell count was a major barrier to prevent mother-to-child transmission of HIV. Thus, in the third quarter of 2011, the Malawi Ministry of Health implemented an innovative approach – Option B+ -. This approach called so by the Ministry of Health postulated that all HIV-infected pregnant and breastfeeding women are eligible for lifelong antiretroviral therapy (ART) regardless CD4 count or clinical stage.

Implementation of Option B+ resulted in a 748% increase in the number of pregnant and breastfeeding women starting ART, from 1,257 in the second quarter of 2011 (representing 5% of all new ART initiations) to 10,663 in the third quarter of 2012 (35% of all new ART initiations).**figure 10**

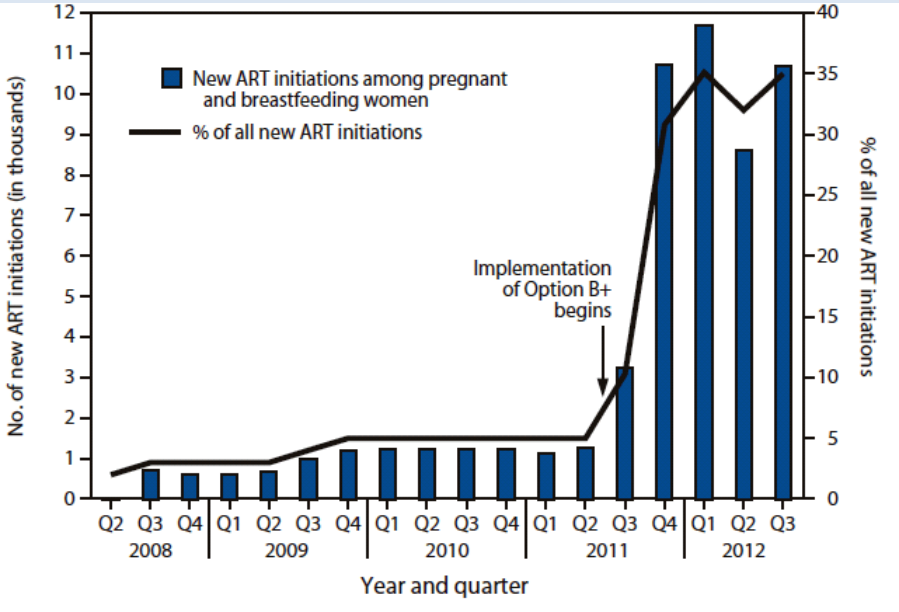

Figure 10. Number of new antiretroviral treatment (ART) initiations among pregnant and breastfeeding women, and percentage of all new ART initiations attributed to this population — Malawi, 2008–2012.

Of the women starting ART in the third quarter of 2011 (the first quarter of Option B+ implementation) who did not transfer care during follow up, 77% continue to receive ART at 12 months. This rate is similar to the 80% 12-month ART retention rate observed among adults who initiated ART in the second quarter of 2011 (the last quarter before Option B+ implementation).

Reference: Center for Disease Control.(2013). Impact of an innovative approach to prevent mother-to-child transmission of HIV-Malawi, July 2011-September 2012. Atlanta, GA, Morbidity and Mortality Weekly Report (MMWR).

5. Research Rationale

Since the last decade, women have been holding the higher burden of HIV epidemic. Current and past global action plans to roll back HIV-epidemic have established that the promotion of gender equality and the eradication of gender-based violence are capital strategies to reduce the spread of HIV epidemic among women.

Although the extent of gender-based violence and, particularly intimate partner violence in sub-Saharan Africa has been subject to a growing amount of scientific research, this topic has been poorly documented in the West African region. The first question we address is to what extent HIV-infected women are victims of gender-based violence, particularly intimate partner physical and sexual violence: ***What is the prevalence rate of intimate partner physical and sexual violence among HIV-infected and HIV-uninfected Togolese women?*** This question has been poorly addressed in the West African region and I believe it is one major input to scale-up the comprehensive HIV-care services.

Secondly, and in line with the goals set out by the global plan of elimination of new pediatric HIV infections and keeping their mothers alive, there is an urgent need to provide quality clinical care to HIV-infected pregnant women, including sexual and reproductive health services. The advent of ART has improved outstandingly the health status of HIV-infected women and pregnancy is not anymore an uncommon event among this population. However, although the incidence rate of pregnancy has been estimated across different settings in sub-Saharan Africa, this epidemiologic parameter has been poorly documented in the West African Region. Thus the second research question of this research framework is: ***what is the incidence rate of pregnancy among HIV-infected women on ART in the West African region?***

Finally, current scientific evidence suggests that pregnancy might represent an important health risk for HIV-infected women. Several studies conducted in sub-Saharan Africa have addressed this question but its conclusions are not definitive. As these studies have been mostly conducted in East and Southern Africa but, this question have been poorly explored in the West African region. The third research question of this research framework is then: ***Is pregnancy associated with a higher risk of death, HIV-disease progression or loss to follow-up among HIV-infected women on ART in West Africa?***

6. Research context: The West African region

6.1. Demographic profile

The West African region is constituted by the 17 more occidental states of the sub-Saharan Africa: Benin, Burkina Faso, Ghana, Guinea, Guinea-Bissau, Côte d'Ivoire, Liberia, Mali, Mauritania, Niger, Nigeria, Senegal, Serra Leone and Togo and the Islands of Cape Verde and Saint Helena which are overseas territories (figure 11).

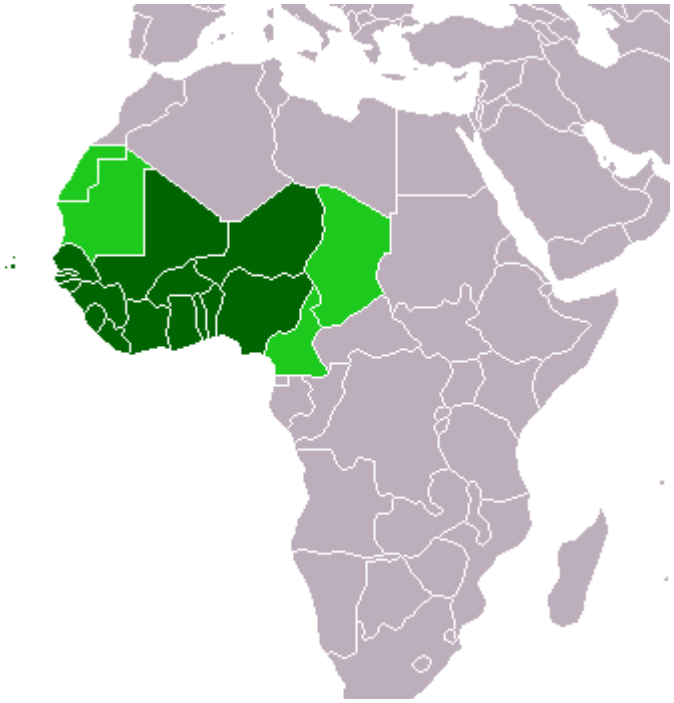

Figure 11. Geographic localization and constitution of the West African Region.

The West African region is confined to an area of 5,112,903 km^2; corresponding to one fifth of the African continent. Limited by the Atlantic Ocean to the West and, by the Saharan dessert to the East and North-East, West Africa is composed of a semi-arid terrain known as Sahel, transitional zone of the Sahara at the north and a belt of tropical forest to the south next to the littoral of the Gulf of Guinea.

Overall, this region accounts for a population of 320 347 000 inhabitants, representing 30% of the whole African population. Nigeria is the seventh most populous country worldwide and accounts for more than a half of the whole west African population.

According to WHO estimations in 2013, the mean life expectancy at birth in the region is 57.2 years, being slightly higher among women(53). The lowest life expectancy is reported by Sierra Leone with 46 years old, whereas in Cabo Verde the overall life expectancy is of 74 years old, the highest of the region(53).

Similarly to other African regions, there are an important number of vernacular languages in West Africa but the official languages of the West African states are French, English and Portuguese. Islam is the most practiced religious cult within the region, followed by Christianity. Although not necessarily official, the animism as a form of cult is commonly practiced within certain West African societies.

6.2. Government system and structures

Excepting five countries (Nigeria, Ghana, Guinea Bissau, Liberia and Sierra Leone), the vast majority of the West African territory belonged to what was called the "French West Africa" constituted by the ancient colonies of the French empire in the African continent. At the end of the last century, all countries of the West African region had achieved their political and economic independence and ever since they have become democratic republics, leaded by a national head of state, elected periodically through citizen participation processes.

In order to promote the economy integration of the west African region and foster the regional collaboration for development, *The Economic Community of West African States - ECOWAS*- (in French: *Communauté économique des États de l'Afrique de l'Ouest* – CEDEAO-), founded in 1975 through the Treaty of Lagos, having as main goal the achievement of collective self-sufficiency for its member states by creating a single large trading bloc through an economic and trading union(54). Ever since ECOWAS is considered one the pillars of the African Economic Community, serving as well as a peacekeeping force for the region operating in three languages: French, English and Portuguese(54).

In addition and consistently with the objectives of ECOWAS, the West African Economic and Monetary Union (UEMOA from the French: Union Economique et Monétaire Ouest Africaine), is a trade bloc of countries composed of an economic union with a monetary union aiming at achieving the economic integration(55). This trade bloc was founded in 1994 with the aim of promoting economic integration among countries that share the CFA franc

as a common currency (Senegal, Benin, Burkina Faso, Côte d'Ivoire, Mali, Niger, Togo and Guinea-Bissau)(55).

Since its foundation, the UEMOA has achieved the successful implementation of an effective regional surveillance system in order to track the regional economic progress. Together with ECOWAS, UEMOA is currently developing a common strategic-action plan on trade liberalization which is expected to turn positively over the economy of the region(54, 55).

6.3. Key economic sectors

The economy of the region is basically supported by two principal activities: exploitation of mineral resources and agriculture. West Africa hosts one the 10th largest oil field of the world located in Nigeria, which is the 12th largest producer of petroleum in the world and the 8th largest exporter(56). Indeed, Nigeria leads the petroleum industry in the sub-Saharan region with proven oil reserve of between 16 to 22 billion barrels(56).

Similarly, the West African region is reach in other precious minerals such as gold and diamonds. Ghana, with a production of 102 metric tons of gold per year is the 7th largest producer of gold worldwide and 2nd largest of Africa, behind South Africa(56). Mali is as well an important gold producer and is considered the third largest in the African continent(56). In addition, Sierra Leone is considered amongst the principal diamond deposits of the world.

The second most important economic activity of the region is agriculture with the culture of cacao, coffee and cotton(57). The cacao industry is leaded by Côte d'Ivoire, with an annual production of roughly 1.5 million tons, the first world producer of this seed(57). Côte d'Ivoire is as well amongst the most important producers of coffee worldwide. The production of cotton is one major activity in the Sahel countries such as Mali and Burkina Faso (57). The production of cereals and other vegetables such as rice, millet, corn, sorghum and peanuts are important key sectors of the economic activities of the region (57).

The industry of telecommunications and technology is rapidly gaining place within the West Africa economic sector, particularly during last years. Nigeria is leading this industry with one of the fastest growing telecommunications markets in the world, basing the major emerging market operator in their country and owing several outer-space satellite units(56). Indeed, Nigeria is the country observing the most impressive and fastest economic growth within the region (56).

However, besides the impressive economic success of Nigeria, the vast majority of the countries of the West African region are categorized as resource-limited countries, with a human development index below the 150th rank (58). Besides Ghana, country classified as medium human development country, the rest of the countries of the region are classified as low human development countries (58).

6.4. HIV epidemic in West Africa

Although HIV infection is highly prevalent across the sub-Saharan Africa region, the distribution of the epidemic varies across the different sub-regions of the continent. Since the early days, sub-Saharan Africa HIV epidemic has been pointed out as generalized, meaning that HIV spreads throughout the general population rather than being confined to populations at higher risk, such as sex workers and their clients, men who have sex with other men or injecting drugs users. Moreover, it has long been recognized that in most countries HIV infection level are higher in urban than in rural areas(14).

In contrast with the high prevalence levels of HIV infection in southern Africa – highest worldwide -, prevalence levels of HIV infection in West Africa is sensibly lower and, varies in scale and intensity comparing to other sub-Saharan regions (figure 16) (13). In 2005, national adult HIV prevalence didn't exceed 10% in any West African country(13). West Africa has been pointed out systematically as the region accounting for the lowest prevalence rates of HIV infection in sub-Saharan Africa (figure 12).

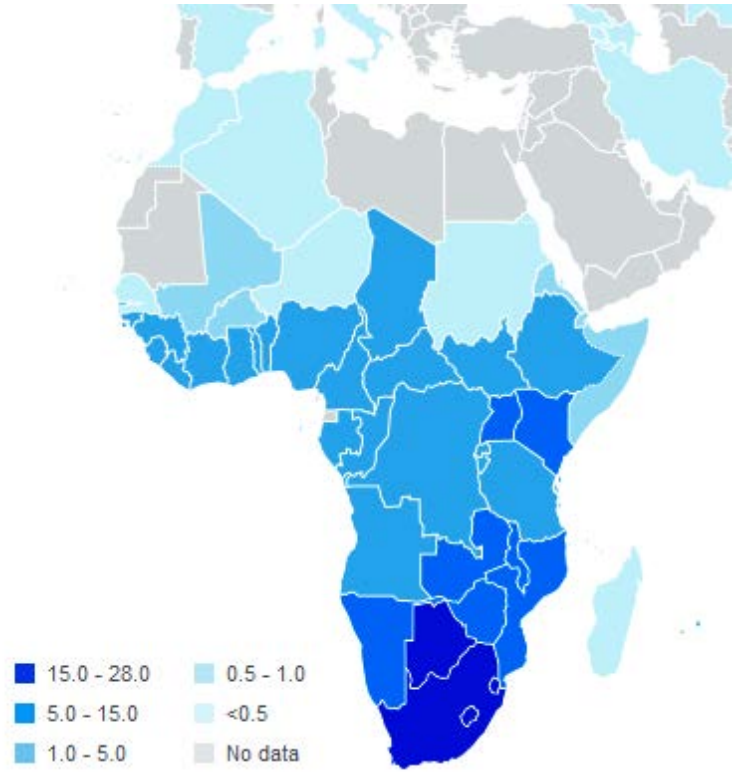

Figure 12. Prevalence of HIV infection in the African continent
(Source: UNAIDS, AIDS info. 2013)

Regional Estimations during mid-twenties described HIV epidemic within West-African region as diverse and changeable (14). In 2004, the prevalence rate of HIV infection in several West African settings was of roughly 2%, keeping a relatively stable epidemiological pattern for almost all 13 countries within the West African region. During late twenties, HIV prevalence within West African sub-region appeared to be much lower than any other sub-Saharan region, finding a relative stability among general population(3, 59, 60).

Although HIV prevalence in West Africa is much lower than anywhere else in the sub-Saharan region, West Africa hosted several serious national epidemics. Nigeria, accounting for a total population of more than 160 million inhabitants, one of the most populous countries in the world, is been hosting a very serious epidemic since early twenties. In 2003, it was estimated that between 3.2 and 3.6 million people were infected with HIV in Nigeria(14). HIV prevalence ranged from 2.3% in the littoral zone to 7% in the north central region among pregnant women (13, 14). Although prevalence rates kept importantly high levels, Nigerian HIV epidemic started to find a relative stabilization at mid-twenties(3). However, Nigeria has still the largest epidemic in the West African sub-region and third largest worldwide, only preceded by India and South Africa(3, 59, 60).

Likewise, available data from Côte d'Ivoire suggested that although the breadth of the national HIV epidemic was smaller than in Nigeria, this West African country faces a serious epidemic. In 2003, prevalence rates levels of HIV infection in Côte d'Ivoire was as high as 7% (range: 4.9–10%)(14). Moreover, epidemiologic surveillance data revealed that HIV prevalence among pregnant women was as high as 10% and 5% in rural and urban settings, respectively (59). However, the difficulties on gathering epidemiologic data during the civil conflict faced by the country during mid-twenties, limits the reliability of these estimations, suggesting an underestimation of the real size of the national HIV epidemic(59). According to UNAIDS estimations, since 2005, the national HIV epidemic in Côte d'Ivoire found a relative stability with a discreet trend to decline. In 2006, prevalence rate of HIV infection among adults observed an important decline of 3% compared to 7% estimated in 2003(13). In 2007, estimations of HIV surveillance among pregnant women indicated that prevalence rate among adult population declined substantially in urban settings, falling from 10% in 2001 to 6.9% in 2005(3, 60). By the end of the decade, prevalence rate of HIV infection among adults declined roughly by the half going from 7% in 2003 to 3.7% in 2009(61).

Besides, Nigeria and Cote d'Ivoire, the rest of the countries seemed to maintain a relatively stable HIV epidemic during the first decade of the century. Epidemiological estimations of the West African region showed almost systematically low prevalence rates among adults of general population(3, 13, 14, 16, 59-61). With the exception of Togo, country which during early twenties reported an HIV prevalence rate of roughly 4% among adult general population, the rest of the countries of the region rarely exceeded a prevalence rate of 2%(59).

In addition, it is important to highlight the particular profile of HIV epidemic in Senegal, country which has been systematically reporting the lowest prevalence rate of the region since early twenties and one of the lowest in sub-Saharan Africa (3, 13, 14, 16, 59-61). Prevalence rates of HIV infection among adults of general population in Senegal have never exceeded 2% across the first decade of the century, reaching rates even below 1%, being the lowest of 0.7% in 2006(60). Senegal is the only country in West African region achieving a successful and sustained control of HIV epidemic among adults of general population during last decade.

6.5. HIV-2 Epidemic

One particular characteristic of the West African HIV epidemic worth to note is the presence of HIV-2 virus. In the late eighties, the prevalence rate of HIV-2 in the region was >1% among the countries of the region(62). These early prevalence rates of HIV-2 have been declining in several West African countries during last years (63-65). The lower size of HIV-2 epidemic has been suggested to be owed to its less efficient transmission rates compared to HIV-1 (66).

Although this virus was more commonly found in the West African region, further epidemiologic assessments point out that HIV-2 has been detected in countries historically attached with West Africa. For example, Portugal where HIV-2 is responsible of 4.2% of all Portuguese in-country AIDS cases (67). In France, out of all new HIV-infections diagnosed between 2003 and 2006, 1.8% were owed to HIV-2(68). Later on, HIV-2 has been also found in other former Portuguese colonies in Africa and worldwide such as Angola, Mozambique, and Brazil. HIV-2 has been also identified In India, particularly in Goa and Maharashtra,

regions having previous attachments to Portugal(66). Presently, HIV-2 has been also identified in the United States or in Europe but mostly among west African immigrants(66).

HIV-2 shares the same mode of transmission of HIV-1, unprotected sexual intercourses, exposure to blood or other biological contagious materials (needles), and mother-to-child transmission. However, scientific evidence shows that infectivity of HIV-2 through any form of transmission path is quite lower than HIV-1 (69-71).

The infection with HIV-2 does not provide immunological protection against contracting HIV-1 and in West-Africa it has been estimated that 0.3% to 1% are dually infected with both HIV-1 and HIV-2(72). HIV-1/2 coinfected patients observed a similar mortality rates as HIV-1 monoinfected patients(73). As the therapeutic regimen of both HIV infections differs, treating coinfected patients is an important clinical challenge.

In addition, HIV-2 infection is characterized by longer asymptomatic period and AIDS progression is slower than HIV-1 infection (74-76). Likewise, although HIV-2 disease is very similar to HIV-1 disease, the progression of HIV-2 disease is highly variable. While some HIV-2-infected patient progress in their disease in the same way HIV-1-infected patients, others progress more slowly, reaching longer asymptomatic periods (77, 78).

To conclude, West Africa has been the region less severely affected by HIV epidemic in sub-Saharan Africa and as anywhere else worldwide the HIV epidemic is composed of two different types of virus: HIV-1 and HIV-2. Current prevalence rates of HIV infections among adults of general population are less than 2% in most of the countries(2, 6). According to recent epidemic estimations, HIV infection rates among the general population are declining and as the number of new infections is decreasing progressively, prevalence rates seems to find a relative stability in general population(6, 18). However, Nigeria and Côte d'Ivoire are the two west African countries hosting serious national epidemics with prevalence rates of roughly 4% in general population, far higher than anywhere else in the region(6).

7. Research platform: International Epidemiologic Databases to Evaluate AIDS – IeDEA Network

The IeDEA network is an international research consortium established in 2005 by the National Institute of Allergy and Infectious Diseases to provide a rich resource for globally diverse HIV/AIDS data. Sites in various regions throughout the world collaborate to collect and define key variables, harmonize data, and implement methodology to effectively pool data as a cost-effective means of generating large data sets to address the high priority research questions and streamline HIV/AIDS research. The NICHD Pediatric, Adolescent, and Maternal AIDS (PAMA) Branch has co-funded the IeDEA since 2006, providing support to allow the inclusion of patient data on infants, children, adolescents, and pregnant women. The National Cancer Institute (NCI), Office of HIV and AIDS Malignancy (OHAM) has provided funding for IeDEA since 2007. This funding supports the collection/analyses of data on cancer, one of the leading co-morbidities of HIV/AIDS.

IeDEA collects HIV/AIDS data from seven international regional data centers, including four in Africa, and one each in the Asia-Pacific region, the Central/South America/Caribbean region, and North America (figure 13). This type of data and resource pooling allows researchers to address unique and evolving research questions that individual cohorts are unable to answer.

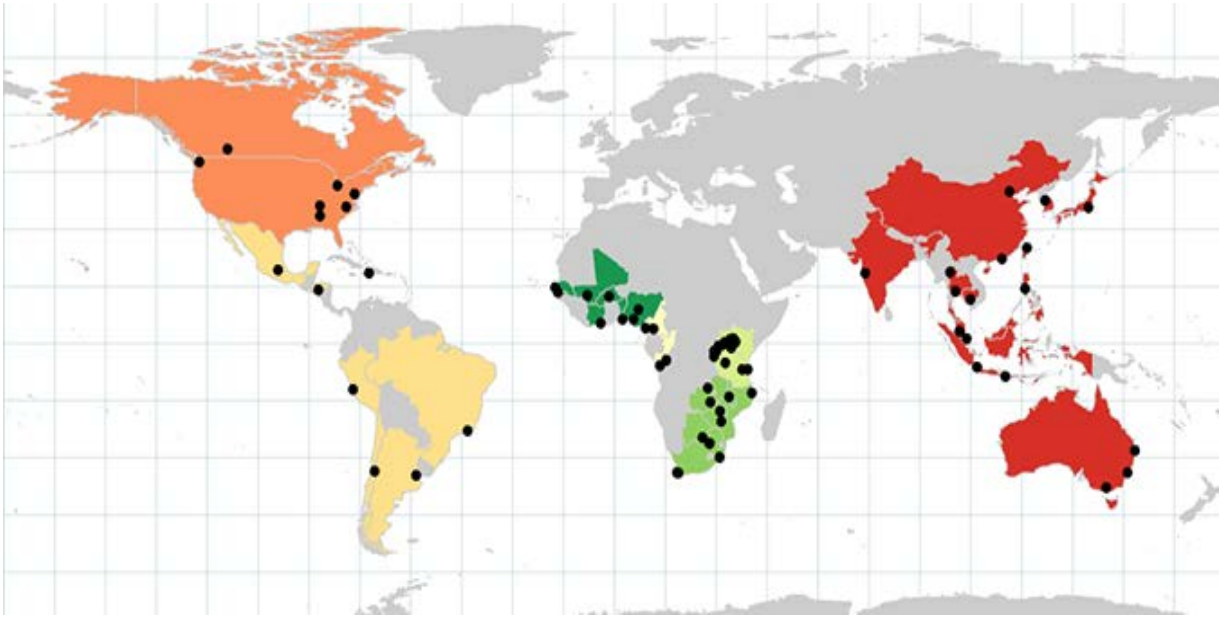

Figure 13. IeDEA Network by regions. (Source: IeDEA. 2014. http://www.iedea.org/)

7.1. IeDEA West Africa regional network

The WADA (West African Data Base on Antiretroviral Therapy) Collaboration is a unique collaboration among cohorts in West Africa with a mission to conduct hypothesis-driven epidemiological research on the prognosis and outcome of HIV type 1 and 2 infected people, including adults, pregnant mothers and children. Participating countries are Benin, Burkina Faso, Cote d'Ivoire, Ghana, Guinea-Bissau, Mali, Nigeria, Senegal and Togo. The collaboration aims at focusing on scientific questions requiring a large sample size. Activities have been focusing initially on cross-sectional analyses of existing data, a comprehensive examination of the available data in terms of completeness of core items at baseline and during follow-up, and the development of instruments to standardize, harmonize and improve data collection across sites.

The research agenda then focused on the following four areas: programmatic issues (access to antiretroviral treatment and losses to follow up); monitoring and outcomes of treatment in adults, children, and pregnant women; clinical response, with a special interest for tuberculosis, opportunistic infections, immune reconstitution syndrome and hepatitis B co-infection; care of HIV-2 infection. A total of 17 cohorts in six major cities in six West African counties – each ongoing and with their own internal governance structure and financial support- have agreed to participate, contributing to more than 5,000 HIV-infected children and 60,000 adults at the end of 2012.

The regional coordinating center is located in Bordeaux, France. This university team has long lasting experience in epidemiological HIV cohort research in West Africa, with an office in Abidjan, Cote d'Ivoire. It also has extensive experience with international collaborations of this kind including the Ghent Group on HIV in Women and Children and the ART-LINC Collaboration. Data are collected from affiliated cohorts every year and once merged into a main WADA database, data extracts are made for the various projects and analyses. This process is repeated annually allowing for the analysis of the most contemporary data collected in the affiliated cohorts. WADA is an unprecedented undertaking in West Africa, with a unique design, led by investigators with extensive experience that will advance the public health knowledge required to better understand and treat HIV-infected persons of all ages, genders and backgrounds in sub-Saharan Africa, the continent with the largest unmet needs but with on-going rapid and massive roll-out of HIV treatment programs.

8. Drivers of HIV infection among women of reproductive age in sub-Saharan Africa

As shown previously, HIV-infection is highly prevalent among women in sub-Saharan Africa, particularly among girls and young women of reproductive age. This phenomenon started to be noticed during early twenties where prevalence rates among this population began to increase rapidly across the region.

Understanding this particular vulnerability of women to acquire HIV infection in sub-Saharan Africa gained rapidly in public health relevance since early twenties. Aiming at rolling back the progression of HIV epidemic, in particular among girls and women, existing scientific evidence aimed principally at measuring the magnitude of the phenomenon within sub-Saharan contexts and, on the other hand determining the different factors probably explaining the rapid spread of HIV epidemic among women in these contexts. In order to reduce the rapid spread of HIV-infection among girls and women, these scientific results have provided stakeholders and policymakers with sufficient information to design and implement preventive strategies aiming at tackling women's-specific high vulnerability towards HIV-infection.

This chapter will firstly present a brief insight of several factors explaining women's vulnerability to acquire HIV infection. The following insight does not pretend to be exhaustive about all existing scientific evidence explaining causality and associated factors of the burden of HIV disease women's are presently shouldering. The content of this section will recapitulate several major biological and psychosocial factors explaining women vulnerability to acquire HIV infection, with a special focus on sub-Saharan Africa.

The present section will be closed with a peer-reviewed article published within this doctoral research framework aiming at estimating the prevalence of intimate partner physical and sexual violence among women according to HIV status in Lomé, Togo.

8.1. Vulnerability of women to contract HIV-infection

Current findings point out that the particular vulnerability of girls and women to acquire HIV infection is owed in part to several women-specific biological factors and in part to several other socio-cultural context-specific factors. Biological factors referred to specificities of women anatomy and physiology that in some extent favor the entrance of the virus into women body. In addition to those women's structural and functional specificities, other associated factors, more related to socio-cultural dynamics of African context which conditioned risk perception and preventive attitudes has been identified as well. Moreover, the possibility of interactions between these different factors has also been suggested. Indeed, gender differences in terms of HIV infection acquisition goes from primary biological sex-specific structures and functions to socio-cultural gender roles and attitudes assigned to women and men defining their social interactions. Taking into account all these factors, African women appeared to be at a higher risk of HIV infection than their male counterparts regardless their socioeconomic and psychosocial status.

8.2. Biological factors associated with women's vulnerability to acquire HIV infection

8.2.1. Anatomic structure of women genitalia

The anatomical configuration of women genitalia has been pointed out as the major biological factor defining women higher risk of contracting HIV infections. Together with several sexual practices, these feminine anatomical particularities are important biological drivers of women's higher risk of contracting HIV infection through a sexual intercourse.

The larger surface of the vagina increases significantly the exposure to infected semen and/or seminal fluids. Additionally, the mucosal barrier of the vagina is constituted of a fragile tissue which can be easily damaged during sexual intercourse, increasing the risk of infection. This vaginal fragility is particularly true for girls, who haven't fully completed their reproductive development(79). Moreover, young women on early stages of physical development are more likely to present an anatomical modification known as cervical ectopy –hormone-induced protrusion of more fragile endocervical columnar epithelium to the cervical portion of the vagina -, leading to a larger more susceptible surface to HIV infection(80-82).

8.2.2. Presence of foreign microorganism in the vaginal environment

The presence of other sexually transmitted diseases or other foreign microorganisms in the surface of the vagina increases significantly the risk of HIV transmission from men to women. Sexually transmitted infections causing ulcers and/or the inflammation produce by these conditions increase importantly the efficiency of HIV transmission by increasing both the infectiousness of and the susceptibility to HIV infection (83, 84). The infection with *candida albicans* or *trichomona vaginalis* may increase the risk of HIV acquisition through cytokines-related inflammatory mechanisms and immune cells impairments possibly increasing susceptibility to acquire HIV infection (85, 86)

On the other hand, vaginal bacterial flora seems to play an important role in women vulnerability to contract HIV infection. Alterations of the delicate biological balance of these microorganisms and vaginal environment may lead to an increased risk of HIV acquisition. Bacterial vaginosis, condition characterized by an imbalance in the ecology of normal vaginal flora, has been consistently associated with an increased risk of HIV infection(87). Bacterial vaginosis is highly prevalent among women in sub-Saharan Africa and is frequently owed to practices and products commonly used by this population to clean and/or change vaginal texture and that may lead to a significant loss of *lactobacilli* or provoke a disruption of the epithelium increasing biological susceptibility to acquire HIV infection(88, 89).

Moreover, seminal fluids are important reservoirs of HIV and major vectors of sexual transmission which are associated with HIV transmission. During acute HIV infection and late stages of HIV disease, seminal viral load increases significantly, increasing proportionally risk of HIV transmission from HIV-infected men to women (90, 91).

8.2.3. Female hormones metabolism: The case of hormonal contraception

Meeting women need for family planning is central to achieve three of the United Nations MDGs – Improving maternal health, reducing child mortality and combating HIV/AIDS – and contributes directly or indirectly to efforts to achieve all the eight goals(92, 93). Family planning provides women with a large range of benefits, improving health, schooling and economic outcomes (94-96). One important short term benefit of safe and effective family planning services helps to prevent unintended pregnancies, reducing the number of abortions, and lower the incidence of pregnancy-related deaths and disability(92, 94).

Despite the enormous health and socioeconomic benefits of family planning, recent scientific evidence suggests that certain methods might be probably associated with the risk of acquiring HIV infection (97-99). However, this evidence is not conclusive and whether various types of hormonal contraception affect the risk of HIV acquisition remains critical question for women's health, principally in populations where HIV is common(100).

Research studies conducted in non-human primates aiming at understanding plausible mechanisms explaining the potential higher risk of HIV acquisition associated with hormonal contraception have suggested several biological hypotheses. Hormonal contraception may probably induce modifications of the configuration of vaginal wall; thinning epithelium layers and thus facilitating virus entrance (101-106). Moreover, it has been also suggested that vaginal normal microbiota is sensible to hormonal changes and vaginal flora imbalances are probably associated with higher risk of HIV acquisition (87, 101, 107, 108). Finally, female sexual hormones are major modulators of vaginal *in situ* immune response, probably increasing the number and the activity of HIV-target cells present in the vaginal epithelium(99, 101, 109-111). It has been suggested that these structural and functional changes favoring a higher risk of HIV-acquisition are more progesterone-related than estrogen-related (101).

On the light of these findings, a growing number of research studies have been exploring these hypotheses among humans. Owed to methodological limitations, findings of these studies are inconclusive. As no scientific evidence was definitive around the whether hormonal contraception increased or not the risk of HIV infection, in 2012, WHO convened a group of experts to review epidemiological, biological, and other data on this issue(112). This group concluded by consensus that WHO should recommend no restriction on use of any method of hormonal contraception for women at high risk of HIV(112). However, the group added a clarification that, because of the inconclusive nature of the evidence relating to progestin-only injectables, women at high risk for HIV who choose progestin-only injectables should be strongly advised to always use male or female condoms and to take other HIV preventive measures(112).

Following this high level expert meeting more recent assessments of current emerging evidence on this concern established that although uncertainty persists regarding whether an association exists between hormonal contraception and the risk of HIV acquisition;

current evidence points out that DMPA (depot medroxyprogesterone acetate) but not NET-EN (norethisterone oenanthate) or COC (combined oral contraceptives pills) use increased women's risk of HIV(113). No data have suggested significantly increased risk of HIV acquisition with use of implants, though data were limited (114). No data are available on the relationship between use of contraceptive patches, rings, or hormonal intrauterine devices and risk of HIV acquisition (114). Thus according to recent guidelines, all women choosing progestin-only injectable contraceptives such as DMPA or NET-EN should be informed of the current uncertainty regarding whether use of these methods increases risk of HIV acquisition, and like all women at risk of HIV, should be empowered to access and use condoms and other HIV preventative measures(114). Randomized clinical trials are now required to conclusively determine whether HC, especially DMPA, increases the risk of HIV acquisition compared to alternative contraceptive methods (113).

To summarize, compared to men, anatomic configuration and physiology of women increase their vulnerability to acquire HIV infection. Vaginal larger surface and the particular fragility of the epithelial tissue covering vaginal walls are effective entry ports to the virus. Alterations of vaginal normal bacterial flora or the presence of pathological microorganisms may lead to immunological changes probably favoring susceptibility to HIV infection. Vaginal tissue is particularly sensible to hormonal activity, which provoke modifications in the epithelial tissue configuration leading to a higher permeability and thus facilitating virus entry. Although these factors increase independently women vulnerability to acquire HIV infection, their interaction with some other context-related sociodemographic factors and psychosocial phenomenon needs to be taken into account.

Box 3. Association of modern contraceptive methods with an increased risk of HIV infection

The role of hormonal contraception increasing the risk of HIV acquisition has been the object of an important number of research studies. Despite the important amount of scientific evidence exploring and explaining the association of hormonal contraception with an increased risk of becoming HIV-infected none of them is conclusive.

In order to formulate accurate and ethicaly correct public health recommendations on the use of contraceptive methods several assessments of current scientific literature has been conducted. With this aim Polis C et al, conducted a systematic review of existing scientific literature which aimed at updating previous existing systematic reviews on hormonal contraception and HIV acquisition in women, incorporating new epidemiological evidence published between December 2011 and January 2014. Whether specific methods of hormonal contraception influence a woman's risk of HIV acquisition was the primary goal of this systematic review. This systematic review was conducted independently of the WHO guidance development process and served as an input to the deliberation of expert group meeting.

Within this systematic review, 22 original research papers were retained as informatives. Consistently with previous reviews, present available evidence suggests that HIV risk acquisition is not increased by oral contraception. However, although the association between injectable contraceptives and HIV risk remain uncertain and inconclusive, new published analyses are consistent with prior scientific evidence suggesting that the use of DMPA lead to a moderate increase of HIV risk acquisition (figure 14).

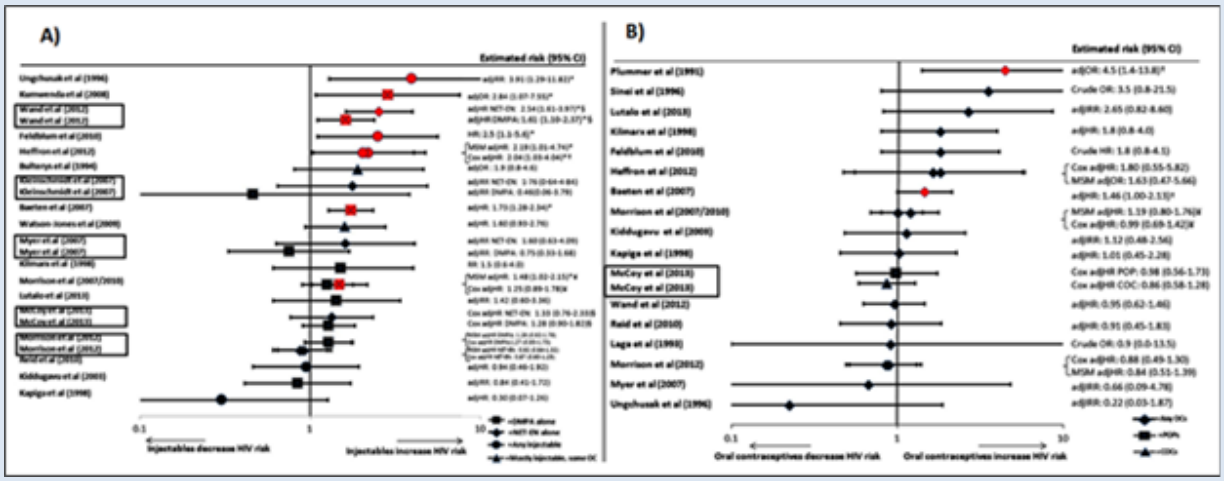

Figure 14. A) Use of injectable contraceptives and HIV acquisition. Error bars show 95% CIs. B) Use of oral contraceptives and HIV acquisition. Error bars show 95% CIs. (Source: Polis, C et al, 2014).

On the light of these findings, current guidelines on the use of Hormonal contraception recommend that women choosing progesting-only injectable contraceptives should be informed of the current uncertainty regarding whether use of these methods is associated with an increased risk of HIV acquisition, and similar to all women at risk of HIV, should be empowered to access and use condoms and other HIV preventive measures.

Reference: *Polis, C. B., S. J. Phillips, et al. (2014). "Hormonal contraceptive methods and risk of HIV acquisition in women: a systematic review of epidemiological evidence." Contraception* ***90****(4): 360-390.*

8.3. Socio-demographic and psychosocial factors driving HIV epidemic among women

The existing literature describes an important number of socio-cultural and psychosocial factors probably explaining the special vulnerability of women to acquire HIV infection. Within this chapter I will make a point on the socio-demographic and psychosocial factors most commonly studied. The order on which the following factors are presented is more sequential rather than hierarchical.

8.3.1. The role of education in the context of HIV epidemic

Besides being a fundamental right of all human beings, education is critical process to develop both societies and individuals. Education ends generational cycles of poverty and disease, providing foundations for sustainable development(115). A quality basic education equips women and men with the necessary knowledge and skills they need to adopt healthy lifestyles, make healthy choices about their sexual behavior and take an active role in social, economic and political decision-making; attenuating the potentially devastating effect of HIV epidemic(115, 116).

Given the relevant role played by education in terms of human development, achieving universal primary education under gender equitable norms has been set out as a part of the MDGs(93). Since this goal has been embraced by the global community in the year 2000, great progress in terms of educational enrolment and attainment has been achieved. In terms of access to education, the achievement have been particularly remarkable in developing regions where school enrolment rate grew from 83% in 2000 to 90% in 2011(93). It is worth to note that, within this period the number of children out of school declined strikingly of roughly the half, 102 Million in 2000 to 57 Million in 2011(93).

However, although the global picture seems to be encouraging, important regional disparities remain. Recent estimations point out that more than half of out-of-school children live in sub-Saharan Africa(93). Although the school attendance rate among schooling-age children increased of roughly 20% within the last ten years in this region, around one quart of the children of schooling age remained out of school in this setting(93). Unsurprisingly, up to date literacy rate in sub-Saharan Africa was of 59%, the lowest worldwide(117)

Moreover, former data also underscored the fact that, with few exceptions, in all regions women literacy rates were lower than male literacy rates(93, 117). Presently, women represents two thirds of illiterate adults worldwide(93, 117). These differences appeared to be more pronounced in sub-Saharan Africa where literacy rates among women barely exceed 50% whereas among men this rate is almost 30% higher(93) (figure 15).

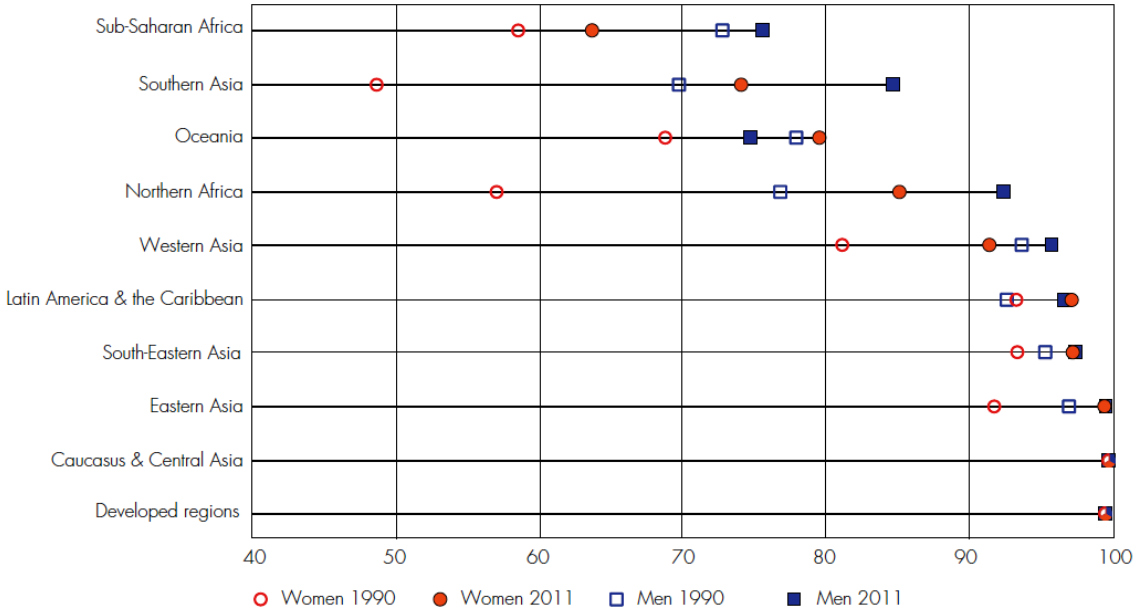

Figure 15. Youth literacy rate by region and by sex, 1990 and 2011 (Percentage)
(Source: The Millennium Development Goals Report 2013)

According to the Global Gender Gap report, sub-Saharan Africa is the region presenting the higher gender gap in terms of educational attainment subindex, with four countries form the region being part of the five lowest performing countries on that subindex, and with thirteen countries out of the bottom 20 countries on the literacy rate indicator(118).

8.3.1.1. Education as a determinant of HIV infection rate among women

The lack of education in terms of quantity and quality has been well documented as a major driver of vulnerability to acquire HIV infection(116). This is particularly true for contexts where access to school education is still far to be universal.

School education, besides being a strategic gateway to introduce knowledge on HIV prevention; it also favors the development of cognitive skills favoring the adoption of safe sexual behaviors. The effect of education on behavior change can be measured in terms of school attendance but also in terms of school attainment (116).

8.3.1.2. The effect of educational attainment in reducing the risk of acquiring HIV infection among women

Several pathways have been suggested through which educational attainment may reduce the risk of HIV acquisition. Firstly, current literature suggests that more educated women are more likely to be exposed to HIV preventive intervention probably increasing safe sexual practices and behaviors (119). Moreover, more educated women are probably more likely to understand the causal relationship between sexual behaviors and HIV acquisition and this understanding probably increase proportionally to school years (120). This means that educated women get to understand more clearly and in a practical way the transmission dynamic of HIV transmission, how to prevent themselves of contracting the infection and adopting more conscious preventive sexual practices(116, 120). Indeed, more educated women are more likely to negotiate safer sex(121), initiate a discussion about family planning with her intimate partner(122) and feel more self-confident about their sexual relationships and practices(123).

Similarly, school attainment plays an important role in terms of developing social networks, which are strongly associated with social norms and individual behavior(116). Among women, sexual faithfulness and practices are significantly related to the number of network partners who also share this same attitudes and practices(124). This suggests that more educated women will tend more significantly to be surrounded by individual of a similar level, probably assuming safer sex practices and therefore having a reduced risk of HIV infection compared to those having a lower level of education(124). In addition, the fact of belonging to a well-functioning social group reduces the risk to become HIV infected by 1.5 times among women (125).

Finally, women attaining higher levels of education tend to delay sexual debut and marriage as well(126). Although staying single and probably sexually active for longer period have been suggested as a potential risk factor for more educated women, this fact is probably compensated by the greater knowledge in terms of HIV prevention this population has (116, 126).

Indeed, according to literature women with at least primary education were more likely to report condom use when compared with their counterpart who didn't reach primary level (116, 120)**.** Similarly, women with secondary education were less likely to report having had

unprotected casual sex and more likely to delay sexual debut (127). Figure 16 explains the mechanisms through which educational attainment reduce the risk of acquiring HIV infection among women.

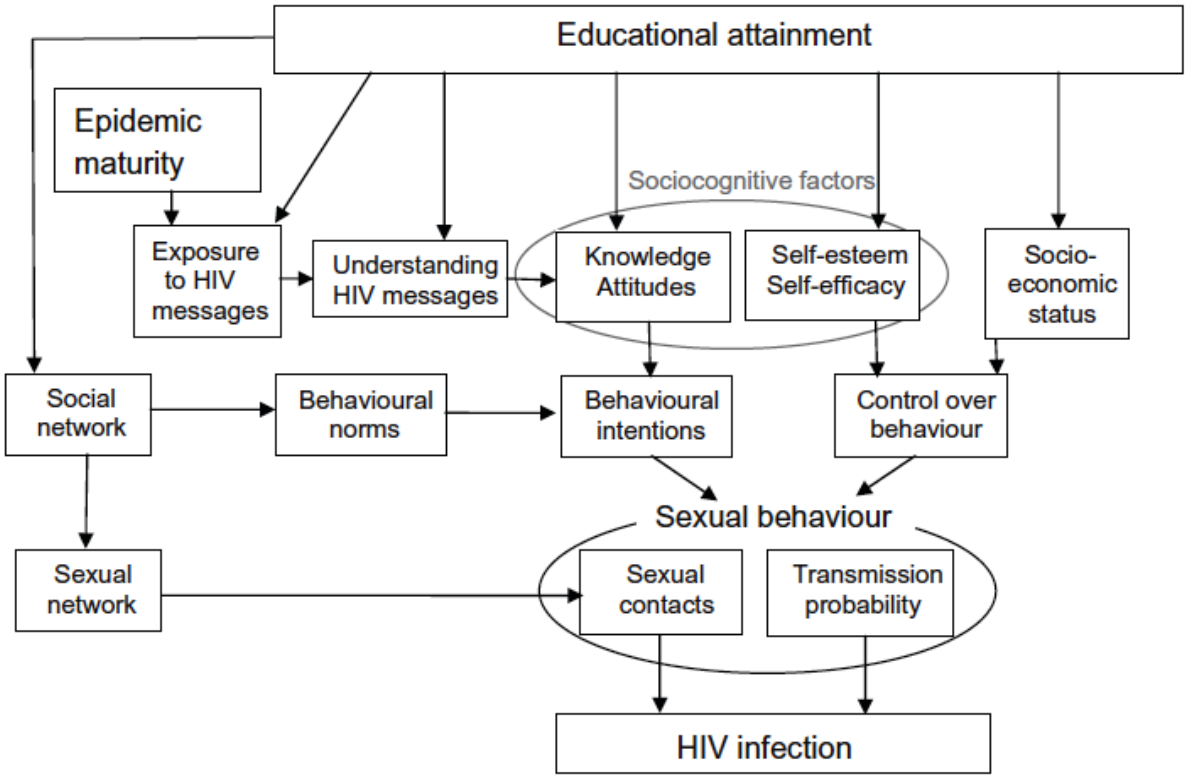

Figure 16. Pathways for the effect of educational attainment on HIV infection. (Source: Jukes et al, AIDS, 2008)

8.3.1.3. The effect of educational attendance in reducing the risk of acquiring HIV infection among women

On the other hand, the mere fact of attending school regardless level of attainment has showed several repercussions in terms of prevention of HIV infection. The mechanisms explaining these repercussions are distinct from the consequences of increased educational attainment discussed above (ref)

Compared with out-of-school young individuals, school pupils have smaller sexual networks, which may reduce the number of potential risk sexual exposures (128). Although often there were no differences in terms of HIV knowledge or access to HIV prevention materials between students and non-students, it has been suggested that students have less risky sexual behaviors and fewer sexual partners than non-students, and this was particularly true

for young school girls (116, 128). Moreover, students attending school have a stronger motivation to avoid consequences of unprotected sex (both pregnancy and HIV infection) when compared to their out-of-school peers (116, 128).

In addition, keeping young girls in schools has been pointed out as a strategy to reduce teenage pregnancy rate which is a reliable indicator of unprotected sexual intercourses(129). Indeed, school girls are 1.5 less likely to have a child, which amounts to nearly a 10% decrease in the childbearing rate for teenagers(129). Moreover, findings of a study conducted in South Africa aiming at comparing sexual behavior between teenaged students and out-of-school teenagers showed up that students tends to have a lower number of sexual partners. Among young women attending to school, a small number reported having sexual partners more than three years older than themselves, having sex more than five times with a partner, and having unprotected sex during the past year(129). These findings suggest that keeping girls in school leads to a reduction in unprotected sex and a reduction in the number of partners which are major risk factors to acquire HIV infection(129).

To summarize, education reduces effectively vulnerability of young people to acquire HIV infection through multiple mechanisms. Increasing the knowledge of young people in terms of prevention, developing skills to adopt preventive measures and behavior, and providing healthier networks are some of the ways through which education reduce young people vulnerability to HIV. Education exerts a HIV preventive effect among young women through two pathways, one measured in terms of education attainment and the other in terms of education attendance. Although both pathways exert a similar effect, they work through different mechanisms. In conclusion, keeping girls in the school and helping them to attain higher levels of education, besides providing them with skills and tools that will improve their socioeconomic status, will help them on taking better reproductive decisions and reducing their risk of acquiring HIV infection.

8.3.2. Age disparate relationships

In settings where poverty is highly prevalent and education lacks of quality, marriage concurs with school attendance and attainment as an alternative pathway to assure women's basic needs (116). In these settings, age-mixing in sexual relationships between younger women an older men are not uncommon as older men are frequently wealthier than their younger counterpart and therefore more up to take in charge women needs.

Unfortunately, findings of research studies in sub-Saharan Africa underscore the fact that HIV infection is more prevalent among older men and this age-disparate relationships are probably one of the sources of the disproportionate rate of HIV between young women and young men (11, 12, 14, 130, 131). This assumption is underpinned by comparison of age-adjusted HIV prevalence data (130) and mathematic modelling (132).

Commonly, for young women, the more important drivers to get involved in a sexual relationship are emotional and material support whereas for boys these drivers are more likely related to social status, not necessarily linked to an economic position (133, 134). These particular drivers observed among young women are probably taking them to be more interested in older men, engaging into so called age-disparate relationships because older men would probably be more likely to fulfill their emotional and material needs (135). Age-disparate relationship, as defined in the literature refers to a gap between partners of five years or more, larger gaps have been classified as intergenerational or cross-generational relationships(135).

The age asymmetries between heterosexual couples have been found to be associated with unsafe sexual behavior, low condom use and therefore an increased risk of HIV infection, particularly among younger women(135, 136). Adolescent's relationship dynamics are characterized by unequal decision-making between partners, lack or poor communication about sexual matters, lack of anticipation of sex and gender-based differences in the motivation to become sexually involved (133). Moreover, it has been suggested that the larger the age difference the greater the association with unsafe sexual practices and HIV infection (135, 137-139). Moreover, these findings suggest as well that for every year's increase in the age difference between partners there was a 28% increase in the odds of having unprotected sex(135, 140).

In sub-Saharan Africa, several factors have been identified within age-disparate relationships that increase the risk of sexually transmitted infections and HIV. Within age-disparate relationships, younger women tend to report a lower risk perception(135). Women in these settings often see older men as "safe" partners because to them, older men appear to be less reckless, more wishful to be in stable relationships and, more responsible and caring for the relationship (135, 141, 142).

Moreover, in sub-Saharan Africa women are often more concerned about the risk of becoming pregnant than of acquiring sexually transmitted infections or HIV (135, 143, 144). In addition, age disparities and economic dependence often compromise women's capacities to negotiate safer sex. For a young women, insisting into the adoption of safe sex practices with older partners is often see as a menace to their economic goals in the relationship(135, 137-139, 141, 145).

According to literature, the reasons explaining why age-disparate relationships between young women and older men are common in sub-Saharan Africa have been suggested to be also context-dependent. Indeed, although the common denominator among young women in a relationship with older men is mostly a matter of economic benefit, the use of this extra income differs whether we explore rural or urban settings.

8.3.2.1. Context-related drivers of age-disparate relationships: in rural settings

The high levels of poverty and the respect of traditional gender roles and attitudes characterizing sub-Saharan Africa rural settings are major drivers of age-disparate and intergenerational relationships among women and men. The lack of access to health services, education and employment; together with the weak economy of rural settings often push girls into age-disparate relationships basically incited by the potential economic benefits(146-149). It is not uncommon in these settings that young women used the material benefit offered by older men to cover their basic needs such as schooling, food and clothing (150, 151). Moreover, it has been suggested that young girls are often encouraged by their parents to get involved in relationships with older employed men as a way to get money and fulfill other household necessities(135).

Owed to the generalized precarious economic situation of rural settings in sub-Saharan Africa, for young women, marriage and motherhood are somewhat effective ways to assure their future socioeconomic security (135). Often young women engage in casual relationships with older men rather than to stablish with them to acquire resources to improve their desirability to potential younger husbands (135). In other words, resources provided by older men help young women to attract and maintain a relationship with

younger men, hopping this will lead to marriage and this is a legitimate manner to assure marriage within certain sub-Saharan Africa societies(144, 149).

Finally and not less important, in rural settings, often young women behavior is predominantly ruled by traditional gender norms. Young rural women are often expected to be obedient and dutiful as a way to show respect towards older men. These attitudes are frequently associated to a higher risk of coercion and sexual violence by older men to engage in sex(135).

8.3.2.2. Context-related drivers of age-disparate relationships: in urban settings

In urban settings, economic benefit is also the major driver for young women to engage into age-disparate relationships with older men, these material benefits are often seen as an additional income to enjoy luxury and status (135). Among urban girls, material gain is the most commonly cited factor motivating they to engage in relationships with older men (135). The second most cited reason is having fun, which is often associated with glamour and the enjoyment of lifestyle consistent with urban context (135). For young women in urban settings, the probability of having their basic needs covered is higher thus economic benefits provided by older partners are mostly received as an accessory income to buy luxury and commodities(135). Moreover, in urban settings, young girls believe that agreeing to engage in unprotected sexual intercourses with an old partner assures a greater economic benefit (152, 153).

Besides economic benefits, for urban young women attracting and maintaining relationships with one or several older wealthy men has also been considered as a mark of cleverness (135, 149). Engaging into a relationship with an older-wealthy man is for young women a mean to achieve goals of personal, familiar and societal success (135). Media has been pointed out as responsible in part of the new self-image young women build of themselves and their beliefs around wealth and success(135). In urban settings, women engaging in age-disparate relationships often perceived themselves as modern empowered women without sexual constraint and great achievers(135). In addition, it is suggested as well that, as in rural settings, families often encourage young women to pursuit this kind of relationships as a mark of personal realization and life success(135).

Anyhow these relationships lead to an exchange of favors in which younger women are not often able to correctly negotiate safe sex practices. Furthermore, several studies have demonstrated a proportional relationship between the benefit and safe-sex practices. The larger the economic transfer of the older partner the less likely is the woman to negotiate safe sex practices(135).

8.3.2.3. Cultural roots of age-disparate relationships

In sub-Saharan Africa is not uncommon to consider girls to be ready for courtship and marriage soon after attaining sexual maturity(135). In order to assure young girls future, being wealth and older than the girl are much appreciated characteristics for a future husband(135). Moreover, older wealthy men are supposed to assume better the authority and family responsibilities(135).

Furthermore, in several African settings girls are often encouraged by their family to marry older men and are aware about the potential difficulties that getting involved with men of similar ages may bring with(135). It is supposed that couples of similar age are not destined to last and short age differences might lead to marriage instability(135). On the other hand, for men in African societies, getting involved with young women is a symbol of virility and vindicates masculinity as defined in these contexts. Moreover, older men often prefer young women because of their presumably higher fertility(135).

In sub-Saharan Africa, age-disparate relationships are often based on reciprocal/transactional interactions within the couple, strengthened by the traditional gender roles and norms of these societies and maintaining the interdependence system. This interdependence system prescribes for men that demonstration of love, commitment and appreciation for sex is in measure of material giving. On the other hand for women, cultural norms prescribe that their worth as women, mother and sexual partner is validated and compensated by material goods. In other words, for women offering sex “for free” is synonym of lack of dignity and self-respect.

The potential economic contribution of older partner is, in some cases used to fulfill basic needs in poor-contexts or, in less-unequitable contexts, just to enjoy a more relaxed and luxurious status. Young women, fearing losing this extra income lose their capacity to negotiate safer sex, believing that acceding to unsafe sexual practices will increase the

material reward. Moreover, in certain contexts, besides the economic benefits women receive by older partners, engaging such relationships is a symbol of success. Anyhow, whatever the motivation is, engaging in age-disparate relationships is a major risk factor for women to acquire HIV infection. This higher risk of acquiring HIV infection within this kind of relationships is explained in part by the higher probability of older men to be infected with HIV and by the limited capacity of young women to negotiate safe sex practices with older partners. To conclude it cannot be excluded the potential risk of physical and sexual violence young women may face when they don't agree with the expected gender norms and attitudes they are expected.

8.4. Gender-based violence: Intimate partner violence

8.4.1. Global background of intimate partner violence

Since the beginning of the century, gender-based violence has been recognized by the global community as the most ubiquitous and serious form of human rights violation worldwide (154-158). It is estimated that one in every five women faces some form of violence during her lifetime, in some cases leading to serious injury or death(157). Around 150 million girls under the age of 18 have experienced some form of sexual violence worldwide, with many never disclosing their traumatic experience(159). Moreover, violence against women is associated with complex social conditions such as poverty, lack of education, gender inequality, child mortality, maternal ill-health and HIV/AIDS (157). Therefore, within the Millennium Declaration, violence against women is recognized as a major threat to social and economic development(160).

Amongst all forms of violence against women, intimate partner violence is the most common and universal form of violence experienced by women and includes physical, sexual, and emotional abuse and controlling behaviors by an intimate partner(161-163). The World Health Organization has proposed the following definitions in order to aid research and programming to correctly identify an measure violent acts perpetrated against women (161):

1. **Intimate partner violence** (also called "domestic" violence) is any self-reported experience of one or more acts of physical and/or sexual violence perpetrated by a current or former partner since the age of 15 years.

a) **Physical violence** means a woman has been slapped, or had something thrown at her; pushed, shoved, or had her hair pulled; hit with a fist or something else that could hurt; choked or burnt; threatened with or had a weapon used against her.
b) **Sexual violence** means a woman has been physically forced to have sexual intercourse; had sexual intercourse because she was afraid of what her partner might do; or forced to do something sexual she found degrading or humiliating.

Though recognized as a serious and pervasive problem, ***emotional violence*** does not yet have a widely accepted definition, but includes, for example, being humiliated or belittled; being scared or intimidated purposefully (161).

An important number of population-based surveys have measured the prevalence rates of intimate partner violence; one notable survey among these is the *WHO multi-country study on women's health and domestic violence against women.* This survey collected data on intimate partner violence of around 24 000 women in 10 culturally and geographically diverse countries around the world. Findings of this population-based survey showed that in almost all settings where this study took place, women were more at risk of violence by an intimate partner than from any other perpetrator (162) (figure 17).

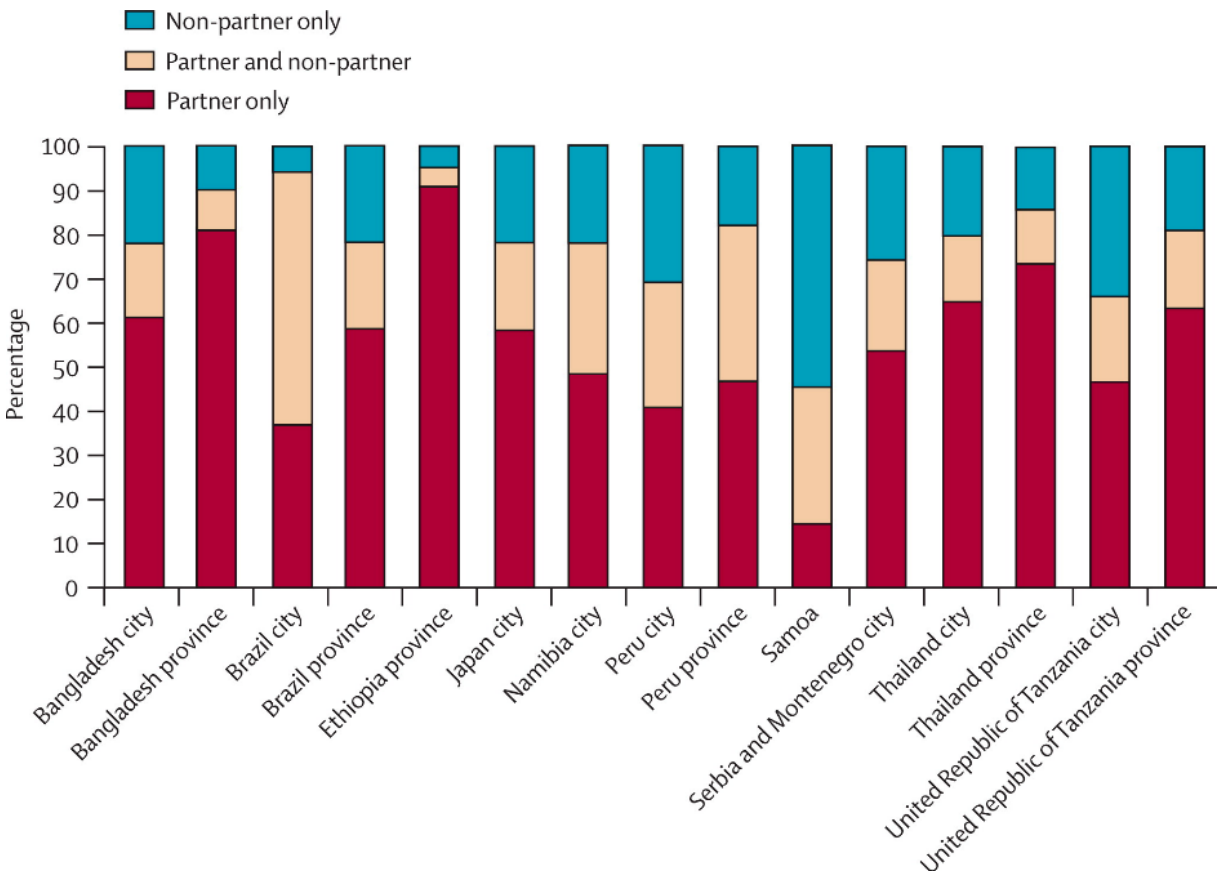

Figure 17. Frequency distribution of partner and non-partner physical or sexual violence, or both, for women reporting such abuse since the age of 15 years, by site (Source: Garcia-Moreno et al. Lancet 2006).

In addition, according to this large population-based survey, global prevalence rates of physical and sexual violence could be as high has 61% and 59% respectively (162). Currently, according to the World Health Organization estimations, about one in three women experience physical and/or sexual violence by an intimate partner (159). In order to guide preventive interventions, current research has explored as well factors associated with this phenomenon.

8.4.2. Factors associated with intimate partner violence

The ecological model is the most broadly used model to understand violence, this model proposes that violence results of factors operating at four different levels: individual, relationship, community and societal. Some risk factors are systematically identified across studies regardless the setting whereas other factors are more contexts specific and vary among and within countries(156, 157, 161).

There are two categories of individual factors associated with intimate partner violence. In the first category are the factors associated with a man's increased likelihood of committing violence against his female partner and the most frequently cited factors are young age, low level of education, witnessing or experiencing violence as a child, harmful use of alcohol and drugs, personality disorders, acceptance of violence, past history of abusing partners(161). On the other hand, the second category is constituted by the factors associated with a woman's increased likelihood of experiencing violence by her partner, within this category the most commonly cited factors are: low level of education, exposure to violence between parents, sexual abuse during childhood, acceptance of violence and exposure to other forms of prior abuse(161).

Relationship-related factors with intimate partner violence, which is the next level are conflict or dissatisfaction in the relationship, male dominance in the family, economic stress, man's concurrent relationships, disparity in educational attainment (161).

At the community and societal level, the following factors have been found associated with an increased risk of intimate partner violence: gender inequitable social norms, poverty, low social and economic status of women, weak legal sanctions against IPV within marriage, lack of women's civil rights, including restrictive or inequitable divorce and marriage laws, weak community sanctions against domestic violence, broad social acceptance of violence as a way to resolve conflict and armed conflict and high levels of general violence in society(161).

8.4.3. Consequences of intimate partner violence

Intimate partner violence has important acute and chronic repercussions on women's mental and physical health (5, 161, 164). In order to explain the mechanism through which intimate partner violence may lead to adverse health outcomes several pathways have been suggested(161) (figure 18).

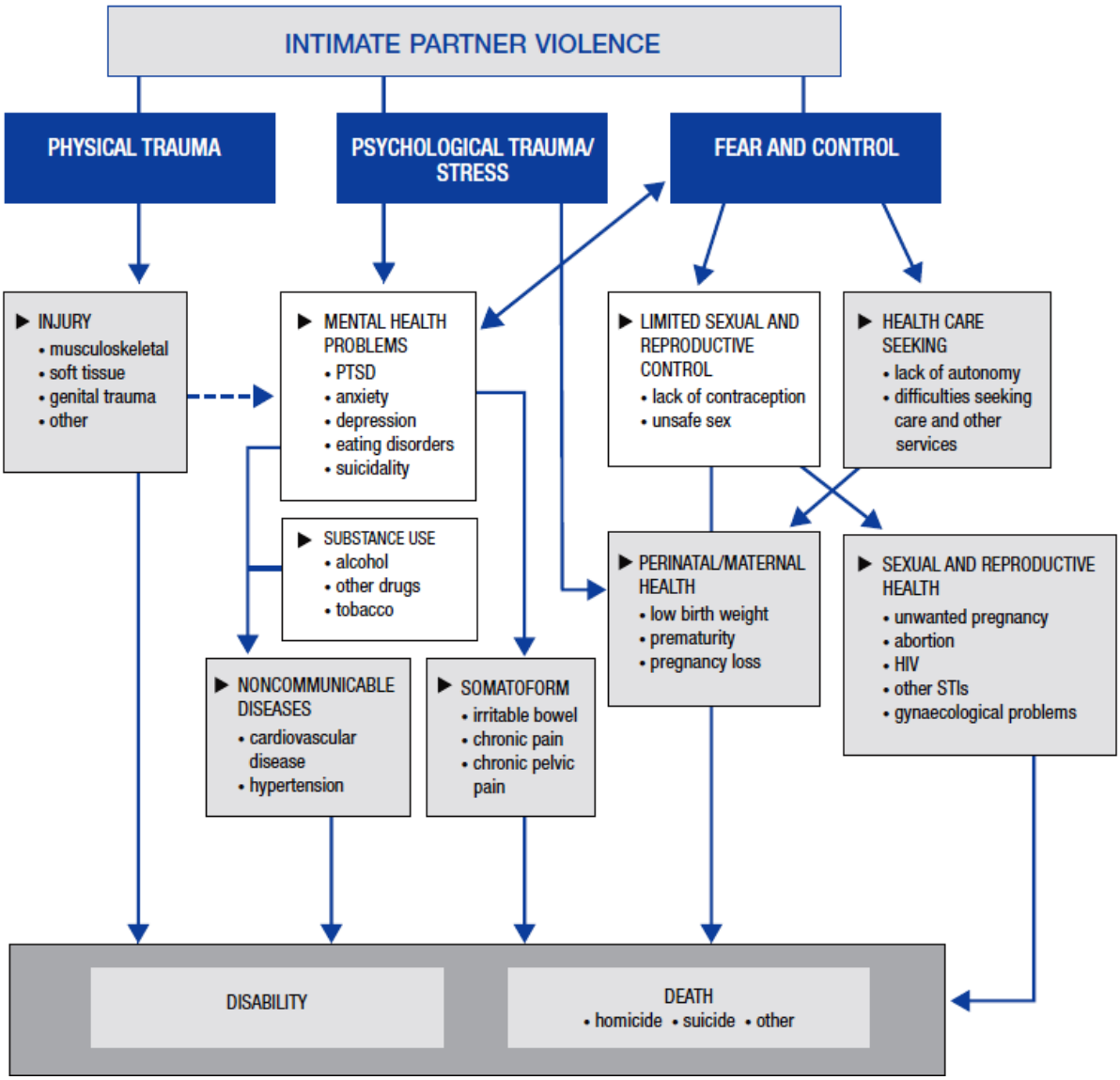

Figure 18. Pathways and health effects on intimate partner violence. (Source: WHO, 2013)

Women suffering of abuse report higher level of depression, anxiety and phobias than their counterparts who have never been victim of abuse(161). According to findings of the WHO multi-country study, women who had experienced physical or sexual violence reported significantly higher levels of emotional distress, thoughts of suicide, and attempted suicide than those who had not experience violence(161, 162). Likewise, intimate partner violence has been also linked to mental and behavioral disorders such as alcohol and drugs abuse, eating and sleeping disorders, poor self-esteem, smoking and unsafe sexual behavior(161, 162).

Moreover, injuries resulting from physical violence can be important sources of handicap and disabilities for women victims (161). In the WHO multi-country study, the prevalence rate of injury among women who had ever been physically abused by their intimate partner could be as high as 55%(162). It is worth to note that, violent acts during pregnancy account for an important proportion of maternal and child mortality, often unrecognized (161, 162).

Intimate partner violence has as well harmful repercussions in sexual and reproductive health including unintended pregnancies, abortions and unsafe abortions and sexually transmitted diseases including HIV(161). The increased risk of acquiring sexually transmitted diseases can be directly associated with coerced sexual intercourses within marriage or indirectly, as women victims of intimate partner physical and sexual violence, are unable to successfully negotiate contraceptive or condom use with their partner(161, 162, 165)

8.4.4. HIV infection: cause and consequence of violence intimate partner violence

Since early nineties, findings of cross-sectional assessments conducted in Africa and South Asia underscore the fact that women victims of physical and/or sexual violence from male intimate partners were more likely to have prevalent sexually transmitted infections, including HIV(165-171). In these settings, intimate partner violence increased the odds of being HIV-infected by almost three times and by about ten times among women under 30 years old(165, 168, 170).

Indeed, women experiencing intimate partner violence were 55% more likely to become infected by HIV (172, 173). This risk appeared to increase proportionally to the severity of this violence (174, 175). The odds were even higher for women who had also experienced sexual abuse in childhood. Those women were 2.5 times more likely to be HIV-positive than women who had never experienced any intimate partner violence nor any childhood sexual abuse(173). The national prevalence of forced first sex among adolescent girls younger than 15 years ranges between 11% and 45% globally(173). In South Africa nearly one in seven cases of people acquiring HIV infection could have been prevented if the women had not been subjected to physical or sexual abuse(173).

More recently, longitudinal research affirmed that young women who had experienced either intimate partner violence and/or high levels of gender inequality in their couple

relationships presented an elevated risk of acquiring HIV (174, 175). These findings suggest a strong causal link between intimate partner violence and HIV infection acquisition(176).

Several pathways explaining the mechanisms through which intimate partner violence increases the risk of HIV acquisition among women victims have been proposed. Firstly, perpetrators of violence are generally considered more likely to be HIV infected because of links observed between violence perpetration, high-risk sex and the use of alcohol and drugs(176). Two main pathways explaining how victims of violence become infected by HIV are proposed. The first pathway is through direct transmission from an infected perpetrator of violence and the second pathway is more related to an increased long term HIV vulnerability resulting from experiences of violence (176) (figure 19).

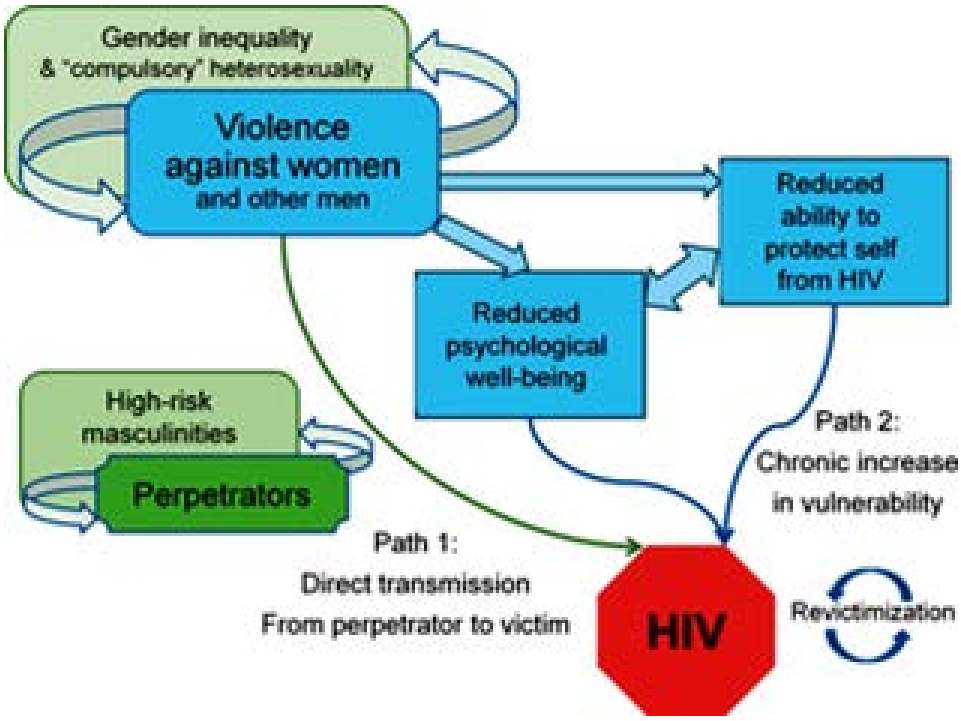

Figure 19. Illustration of pathways from gender inequality and high-risk masculinity to increased HIV risk among survivors of violence. (Source: *Dunkel et al, Am J Reprod Immunol, 2013*)

Furthermore, current research point out as well that intimate partner violence is highly prevalent among HIV-positive women. Findings of several studies suggest that women are more likely to experience intimate partner violence if they are known to be living with HIV (165, 173). This increased likelihood of HIV-positive women to be victims of intimate partner violence is regardless geographic location and socioeconomic status. In a study conducted by Dhairyawan et al in United Kingdom findings showed that more than the half of HIV-positive

women interviewed reported that they had experienced intimate partner violence, one in every seven had experienced it within the past two months alone(177). Findings of this study also underscored that women reported increased violence following their HIV diagnosis or disclosure (173, 177). Likewise, findings of a large study conducted by Silverman et al in India showed that prevalence rates of HIV infection were significantly higher among married Indian women experiencing both physical and sexual violence from husbands compared to those not experiencing intimate partner violence (0.73% vs 0.19%; adjusted OR, 3.92; 95% CI, 1.41-10.94; P = .01)(170). The People Living with HIV Stigma Index shows that women living with HIV in the Asia-Pacific region are more likely than men living with HIV in the same region to be the target of verbal abuse and physical violence as a direct result of their HIV status(178).

To summarize this section, we retain that intimate partner violence is the most frequent form of violence women face. Although intimate partner violence is highly prevalent worldwide, it appeared to be higher in low-and-middle income settings. Intimate partner violence has been associated with important negative health consequences and important risk factor to acquire HIV infection. Moreover, among women, an HIV positive status has been associated with a higher risk of being victim of intimate partner violence. Although the prevalence rate of intimate partner physical and sexual violence has been documented in several sub-Saharan African settings, this indicator is scarcely documented in the West African region. Scientific findings of the following peer-reviewed article are amongst the first published reporting prevalence rates of intimate partner physical and sexual violence in the West African region.

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Global Health Action

GENDER AND HEALTH

Intimate partner sexual and physical violence among women in Togo, West Africa: Prevalence, associated factors, and the specific role of HIV infection

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Background: A substantial proportion of newly diagnosed HIV infections in sub-Saharan Africa occur within serodiscordant cohabiting heterosexual couples. Intimate partner violence is a major concern for couple-oriented HIV preventive approaches. This study aimed at estimating the prevalence and associated factors of intimate partner physical and sexual violence among HIV-infected and -uninfected women in Togo. We also described the severity and consequences of this violence as well as care-seeking behaviors of women exposed to intimate partner violence.

Methods: A cross-sectional survey was conducted between May and July 2011 within Sylvanus Olympio University Hospital in Lomé. HIV-infected women attending HIV care and uninfected women attending postnatal care and/or children immunization visits were interviewed. Intimate partner physical and sexual violence and controlling behaviors were assessed using an adapted version of the *WHO Multi-country study on Women's Health and Life Events* questionnaire.

Results: Overall, 150 HIV-uninfected and 304 HIV-infected women accepted to be interviewed. The prevalence rates of lifetime physical and sexual violence among HIV-infected women were significantly higher than among uninfected women (63.1 vs. 39.3%, $p < 0.01$ and 69.7 vs. 35.3%, $p < 0.01$, respectively). Forty-two percent of the women reported having ever had physical injuries as a consequence of intimate partner violence. Among injured women, only one-third had ever disclosed real causes of injuries to medical staff and none of them had been referred to local organizations to receive appropriate psychological support. Regardless of HIV status and after adjustment on potential confounders, the risk of intimate partner physical and sexual violence was strongly and significantly associated with male partner multi-partnership and early start of sexual life. Among uninfected women, physical violence was significantly associated with gender submissive attitudes.

Discussion and conclusions: The prevalence rates of both lifetime physical and sexual violence were very high among HIV-uninfected women and even higher among HIV-infected women recruited in health facilities in this West African country. Screening for intimate partner violence should be systematic in health-care settings, and specifically within HIV care services. At a time of increased investments in couple-oriented HIV prevention interventions, further longitudinal research to better understanding of HIV-serodiscordant couple dynamics in terms of intimate partner violence is needed.

Keywords: *intimate partner violence*; *gender*; *HIV infection*; *Africa*

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According to the World Health Organization (WHO), intimate partner violence is defined as the behavior, within an intimate relationship, that causes physical, sexual, or psychological harm or suffering (1). Several population-based surveys have reported that among all forms of violence against women, intimate

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partner violence is the most prevalent and it is considered the most common human rights violation hitherto (2, 3). Although there is still insufficient consensus on the operational definition and measurement of intimate partner violence, available estimations of lifetime prevalence of intimate partner violence vary from 15 to 71% worldwide, with the highest rates documented in resource-constrained settings (4). Intimate partner violence is associated with poor health outcomes among victims and is therefore a major public health issue (5–7).

Besides its dramatic physical and mental consequences, intimate partner violence has also been identified as an important risk factor for sexually transmitted diseases acquisition and particularly HIV infection (8). Intimate partner violence and HIV infection are linked by a very complex association, including diverse pathways. An increased risk of HIV transmission within abusive relationships and a greater likelihood of acquisition of HIV infection by violent husbands have been reported (8, 9). Acts derived from intimate partner violence, such as coerced sexual intercourse, during which women are unable to protect themselves from transmission, place women at direct risk of HIV infection (10).

Sub-Saharan Africa is the region reporting the highest epidemiological burden of HIV worldwide, with women accounting for 58% of newly acquired HIV infections (11). Furthermore, HIV infection in these settings spreads principally through heterosexual transmission and a substantial proportion of newly diagnosed infections occur in HIV-discordant cohabiting couples in which only one person is living with HIV (12). HIV prevention interventions aiming at protecting both couple members are thus a public health priority to reduce HIV incidence in these regions and several approaches have been already proposed (10–14). In spite of their proven efficacy, the challenges in implementing couple-oriented HIV preventive approaches are tremendous, and most importantly because they are based on mutual disclosure of HIV serological status (14–17). Intimate partner violence as one important consequence of HIV serological disclosure is thus one major limit of couple-oriented HIV preventive approaches and understanding its magnitude, dynamics, and factors associated are a prerequisite to the roll out of these couple strategies (1, 10, 12, 13).

In Togo, a West African country with an estimated prevalence rate of HIV infection of 3.4% nationwide and a predominantly heterosexual epidemic (11), intimate partner violence among women and its association with HIV infection has never been studied so far using a quantitative methodological approach, to the best of our knowledge. Moreover, data on intimate partner violence according to serological status in the West African region are very scarce, although it is needed to improve the scaling-up of HIV prevention, care, and treatment programs. This study aimed at estimating the prevalence and associated factors of intimate partner physical and sexual violence among HIV-infected and -uninfected women of childbearing age attending a clinical facility in Togo. We also described the severity and consequences of this violence as well as care-seeking behaviors of women exposed to intimate partner violence.

Methods

Study design and population

This project was an international collaboration between the INSERM (National Institute of Health and Medical Research) Research Centre U897 based in Bordeaux (France), the Sylvanus Olympio University Hospital in Lomé, and the non-governmental organization *Espoir Vie Togo*, one leading organization providing care and psychological support to people living with HIV/AIDS in Togo.

A cross-sectional survey was conducted between May and July 2011 within the Lomé University Hospital. The study population was constituted by volunteer participants attending clinical services in the hospital. HIV-infected women attending regular HIV care visits constituted the first group. Women attending postnatal care and/or children immunization visits, and who had been diagnosed HIV-uninfected during their last pregnancy, constituted the second group. For these two study groups, women aged at least 18 years, declaring having a current intimate partner or having ever had one, were eligible to recruitment.

Study procedures

The survey was conducted in three stages. The first preparatory phase consisted of a methodological workshop between Togolese and French researchers to discuss the study design, validate the survey instruments, and address relevant ethical issues. A local team of four psychologists was recruited to adapt concepts described in the questionnaires to the local context, train interviewers on the study tool, ethical and privacy terms, and supervise data collection.

Second, a pilot study was carried out to test the acceptability, adequacy, and understandability of the recruitment procedures and questionnaire. Survey feasibility data and interviewer's observations were integrated within the final survey procedures and tools.

Finally, every working day during the study period, each eligible woman was systematically asked to participate in the survey and to provide signed informed consent to be sequentially enrolled. Trained female health-care staff administered the questionnaire during a 20-min face-to-face interview in a private room.

All interviews were carried out in French, and all participants were provided information about local support services dedicated to women experiencing intimate

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partner violence. HIV-infected women were informed about the psychological support available at *Espoir vie Togo*.

The study protocol was approved by the National Ethic Committee of the Ministry of Health of Togo (N°0125/2011/MS/CAB/DGS/DPLET/CBRS). Written informed consent was obtained from all participants; and all data collection tools were strictly anonymous.

Intimate partner physical and sexual violence assessment

Our questionnaire assessing intimate partner physical and sexual violence and controlling behaviors was largely inspired by the *WHO Multi-Country Study on Women's Health and Life Events* questionnaire (version 10) (4, 18, 19).

All women participating in the survey were asked about their life experience on specific acts of physical and sexual violence induced by their intimate partner. Physical violence was defined as the use of physical force causing bodily harm (1). Within the survey, women were also asked about physical consequences of physical violent acts induced by an intimate partner, as well as help-seeking behaviors. Sexual violence was defined as any situation where women faced forced or coerced sexual act or attitude (1). Prevalence of physical/sexual violence was estimated as the proportion of women declaring having been exposed to any kind of physical or sexual violent act by their current intimate partner or any previous partner.

Additionally, we explored attitudes toward partner controlling behaviors that we summarized in six statements, illustrating different gender submissive situations to which women were asked to agree or not. We developed a scoring system to define a 'submission index' summarizing women's attitudes toward partner controlling behaviors based on the sum of the number of positive answers to six questions detailed in Table 1.

We also documented women's sociodemographic characteristics (age, instruction level, and contraceptive use), data on the women's partner (alcohol consumption and frequency of involvement in fights) and couple relationships (polygamy and concurrent relationship), women's employment and financial autonomy (having a financial autonomy to support herself and household without her partner for at least 1 month), and the modalities of women's entry in sexual life (conditions and age at first sexual intercourse). We also investigated women's mental health (loss of interest, suicidal thoughts, and suicidal attempts) and the history of non-partner violence (physical violence after 15 years and sexual violence before and after 15 years).

Statistical analysis

Sociodemographical and psychosocial characteristics of women and partners were described and compared between HIV-infected and -uninfected women. Maternal age was dichotomized into two categories with a cut-off defined by the median in the overall population (e.g. 33 years). Age of first sexual intercourse was dichotomized into two categories with a cut-off defined by the age at sexual majority in Togo (e.g. 18 years). The prevalence of lifetime physical and sexual violence was estimated separately among HIV-infected and -uninfected women and also compared between the two groups. Chi-square tests were performed to determine statistically significant differences. Sociodemographic and behavioral factors associated with lifetime physical and sexual violence in both groups were then assessed using logistic regression. Both univariate and multivariate analyses were carried out. Variables found to be statistically associated with intimate partner violence with a p-value of <0.25 were included in the multivariable model. To select the final adjusted model presented in this paper, we used a backward elimination method using a p-value of 0.05 (20). Adjusted odds ratios (aORs) were estimated using multiple logistic regression modeling and statistical significance was considered at the 5% level. Statistical analyses were generated using SAS software (version 9.2 for Windows, Copyright 2013 for SAS Institute Inc., Cary, NC, USA).

Results

Overall, 454 women attending the Sylvanus Olympio University Hospital were informed about the study and screened for eligibility; all of them accepted to be interviewed and were included in the study. One hundred and fifty women were HIV-negative and 304 were HIV-positive.

Study population characteristics

Sociodemographical and behavioral characteristics of women in both groups are described in Table 1 and summarized as follows.

Concerning women's sociodemographic profile and financial autonomy, HIV-infected women were significantly older than uninfected women (35 [32–37] and 30 [29–34] years old in median [interquartile range], respectively, $p<0.01$). The proportion of HIV-uninfected women having completed at least primary education was significantly higher than among HIV-positive women (94.7 vs. 83.9%, $p=0.01$). HIV-infected women were significantly more likely than uninfected women to report some degree of financial autonomy (56 vs. 39.3%, $p<0.001$). HIV-uninfected women were more likely to be using a contraceptive method at the time of the survey than HIV-infected women (64.7 vs. 42.1%, $p\leq0.001$).

Concerning modalities of entry to sexual life, the proportion of women having entered sexual life before the age of 18 was higher among HIV-infected than HIV-negative women (62.8 vs. 58.0%, $p=0.32$). HIV-infected women were significantly more likely to start sexual life

Table 1. Characteristics of women interviewed according to their HIV status: Lomé, Togo, May–July 2011

	HIV uninfected (N = 150)		HIV infected (N = 304)		
	n	%	*N*	%	*p*
Women's sociodemographic profile					
Age					
≥33 y/o	55	36.7	185	60.9	<0.01
<33 y/o	95	63.3	119	39.1	
Instruction level					
Not instructed	8	5.3	49	16.1	0.01
At least primary level	142	94.7	255	83.9	
Contraceptive method[a]					
Yes	97	64.7	128	42.1	<0.01
No	53	35.3	176	57.9	
Financial autonomy					
Employment					
Yes	103	68.7	242	79.6	0.01
No	47	31.3	62	20.4	
Financial autonomy to support herself[b]					
Yes	59	39.3	170	56.0	<0.01
No	91	60.7	134	44.0	
Modalities of entry to sexual life					
Age of first sexual intercourse					
≥18 y/o	63	42.0	113	37.2	0.32
<18 y/o	87	58.0	191	62.8	
Conditions of first sexual intercourse					
Consented	121	80.7	209	69.4	0.01
Coerced	29	19.3	92	30.6	
Women's mental health					
Loss of interest[c]					
Yes	103	68.7	225	74.0	0.23
No	47	31.3	79	26.0	
Suicidal thoughts[d]					
Yes	36	24.0	157	51.6	<0.01
No	114	76.0	147	48.4	
Suicidal attempts[d]					
Yes	8	5.3	23	7.6	0.37
No	142	94.7	281	92.4	
Partners profile					
Polygamous					
Yes	19	12.7	138	45.4	<0.01
No	131	87.3	166	54.6	
Concurrent relationships					
Yes	52	34.7	203	66.8	<0.01
No	98	65.3	101	33.2	
Alcohol consumption					
Never/occasionally	85	56.7	125	41.0	0.01
Frequently	65	43.3	179	59.0	
Frequently involved in fights/riots					
Yes	11	7.3	65	21.4	<0.01
No	139	92.7	239	78.6	

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Table 1 (*Continued*)

	HIV uninfected (N = 150)		HIV infected (N = 304)		
	n	%	*N*	%	*p*
History of non-partner violence					
Physical violence after 15 y/o					
Yes	60	40.0	200	65.8	<0.01
No	90	60.0	104	34.2	
Sexual violence after 15 y/o					
Yes	1	0.7	11	3.6	0.06
No	149	99.3	293	96.4	
Sexual violence before 15 y/o					
Yes	6	4.0	41	13.5	0.01
No	144	96.0	263	86.5	
Controlling behaviors and submission index					
A good wife obeys her partner, even if she does not agree with him					
Yes	113	75.3	278	91.5	<0.01
No	37	24.67	26	8.55	
It is important that a man shows his wife who is the boss?					
Yes	104	69.3	240	78.9	0.02
No	46	30.7	64	21.0	
A woman may have the freedom to choose her friends, even if her partner does not agree?					
Yes	19	12.7	49	16.1	0.33
No	131	87.3	255	83.8	
Satisfying her husband's sexual desire even if she does not want to is a women's duty?					
Yes	46	30.7	151	49.7	<0.01
No	104	69.3	153	50.3	
If a man abuses his wife, people around must intervene?					
Yes	122	81.3	240	78.8	
No	28	18.6	64	21.1	
A man must strike his wife if he considers this necessary?					
Yes	49	32.7	174	57.2	<0.01
No	101	67.3	130	42.7	
Submission index					
Median	3		4		<0.01

[a]Use of any contraceptive method at the moment of the survey.
[b]Having a financial autonomy to support herself and household without her partner for at least 1 month.
[c]During at least two weeks over the last 12 months.
[d]At least once over the last 12 months.

through a first forced sexual intercourse than uninfected ones (30.6 vs. 19.3%, $p = 0.01$).

Concerning partner's profile characteristics, HIV-infected women were more likely to live within polygamous households than uninfected women (45.4 vs. 12.7%, $p < 0.001$) and to declare that their partner had concurrent relationships out of the household (66.8 vs. 34.7%, $p < 0.001$). Reported rates of partner alcohol consumption (59.0 vs. 43.3%, $p = 0.01$) and partner involvement in fights and riots (21.4 vs. 7.3%, $p < 0.001$) were more frequent among HIV-infected women than uninfected women.

Concerning women's mental health, suicidal thoughts during the past 12 months were significantly more frequent among HIV-infected women than among the uninfected ones (51.6 vs. 24.0%, $p < 0.001$). The proportion of HIV-infected women reporting loss of interest

(74.0 vs. 68.7%; $p = 0.23$) and suicidal attempts (7.6 vs. 5.3%, $p = 0.37$) during the past 12 months tended to be higher than among uninfected ones but differences were not statistically significant.

Finally, HIV-infected women were slightly more likely to agree to submissive statements than HIV-uninfected women (scoring of 4/6 and 3/6, respectively; $p < 0.001$).

Intimate partner violence: prevalence, severity, and care-seeking behaviors

As detailed in Table 2, the prevalence rate of lifetime physical violence among HIV-infected women was 63.1% (95% CI: 57.5–68.4), significantly higher than among uninfected women (39.3%; 95% CI: 31.1–46.8; $p < 0.01$). Similarly, HIV-infected women reported a significantly higher prevalence rate of lifetime sexual violence compared to the uninfected ones (69.7%; 95% CI: 63.8–74.1 vs. 35.3%; 95% CI: 27.3–42.6; $p < 0.01$). The lifetime prevalence rate of both types of violence combined (physical and sexual violence) was 51.6% (95% CI: 45.3–56.6) among HIV-infected women and significantly higher than among uninfected women (18.6%; 95% CI: 11.8–24.1; $p < 0.01$; Table 2).

HIV-infected women were more likely to report a history of physical violence after the age of 15 than HIV-uninfected women (65.8 vs. 40.0%; $p < 0.001$) and the frequency of sexual violence during childhood (before 15 years old) was 13.5% among HIV-infected versus 4.0% among uninfected ones ($p = 0.01$; Table 1).

Among women ever victims of intimate partner physical violence ($n = 251$), 194 (77.2%) reported physical injuries as a consequence of this violence (Table 3). Most commonly reported injuries were scratches and bruises (80.9%), dislocation and sprains (62.9%), eardrums rupture and black eyes (54.6%), penetration injuries and deep cuts (28.9%), and gashes and bites (20.1), although less commonly reported were burns (5.7%), fractures (4.6%), and broken tooth (1.6%). There were no differences between the type of injuries reported by HIV-infected and -uninfected women (data not shown).

Among the 194 women reporting being injured by intimate partner violence, 160 (82.4%) reported needing medical care for their injuries. From those needing medical care, 93 (58.1%) received medical care and 14 (7.2%) were even hospitalized. Among injured women in care, 49 (52.6%) disclosed real causes of injuries to medical staff and none of them was referred to local organizations to receive appropriate psychological support (Table 3).

Factors associated with physical violence

The only common factor associated with a history of intimate partner physical violence regardless of women's serological status was having a partner maintaining concurrent relationships out of the household (HIV-uninfected: aOR: 2.5; 95% CI: 1.1–5.5; $p = 0.02$, and HIV infected: aOR: 2.2; 95% CI: 1.3–3.6; $p < 0.001$). Otherwise, the profile of HIV-infected and HIV-negative women reporting intimate partner physical violence was different (Table 4).

Among women's sociodemographic and sexual characteristics, age was associated with physical violence only for HIV-uninfected women (33 years old or below vs. older than 33 years: aOR: 0.4; 95% CI: 0.2–0.9; $p = 0.02$), and education level only for HIV-infected women (at least primary level vs. never attended school: aOR: 2.0; 95% CI: 1.0–4.2; $p = 0.05$). Uninfected women not using any contraceptive method at the time of the survey were more likely to be victims of intimate partner physical violence (aOR: 2.3; 95% CI: 1.0–5.0; $p = 0.04$). Among uninfected women, the odds of intimate partner sexual violence were significantly higher among those reporting a first coerced sexual intercourse (aOR: 2.6; 95% CI: 1.1–6.6; $p = 0.04$).

In terms of women's mental health status, having ever attempted suicide was strongly associated with a history of intimate partner physical violence, for HIV-infected women only (aOR: 4.5; 95% CI: 1.3–15.9; $p = 0.02$). In the univariate analysis, loss of interest during at least

Table 2. Lifetime prevalence rates of intimate partner violence (physical, sexual, and both types of violence) among women, according to their HIV status: Lomé, Togo, May–July 2011

	HIV uninfected, $N = 150$			HIV infected, $N = 304$		
	n	%	95% CI	*n*	%	95% CI
Any form of physical violence						
Yes	59	39.3	31.1–46.8	192	63.2	57.5–68.4
No	91	60.7	52.1–67.8	112	36.8	30.6–41.3
Any form of sexual violence						
Yes	53	35.3	27.3–42.6	212	69.7	63.8–74.1
No	97	64.7	56.3–71.6	92	30.3	24.8–35.1
Any form of physical and sexual violence combined						
Yes	28	18.7	11.8–24.1	157	51.6	45.3–56.6
No	122	81.3	74.7–87.2	147	48.4	42.3–53.6

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Table 3. Distribution of physical injuries and care-seeking cascade reported by women victims of physical violence: Lomé, Togo, May–July 2011

	N	%
Number of physically injured women among those victims of physical violence (n = 251)	194	77.2
Types of physical injuries reported (n = 194)		
Scratches, hematomas	157	80.9
Dislocation, sprains	122	62.9
Eardrums rupture, black eyes	106	54.6
Penetration injuries, deep cuts, gashes	56	28.9
Bites	39	20.1
Burns	11	5.7
Fractures, broken bones	9	4.6
Broken teeth	3	1.6
Hospitalizations	14	7.2
Number of injured women needing medical care after being injured (n = 194)	160	82.4
Number of injured women having received medical care when injured (n = 160)	93	58.1
Number of women that told medical personnel the real cause of injuries (n = 93)	49	52.6
Number of women referred to a dedicated support group (n = 49)	0	0.0

two weeks (OR: 2.9; 95% CI: 1.7–4.9; $p < 0.001$) and having had suicidal thought at least once over the last 12 months (OR: 1.7; 95% CI: 1.1–2.8; $p = 0.02$) were also associated with having experienced intimate physical violence among HIV-infected women.

Factors associated with sexual violence

As detailed in Table 5, starting sexual life before the age of 18 appeared to be the only common factor associated with intimate partner sexual violence among both HIV-infected and -uninfected women (HIV-infected women: aOR: 2.3; 95% CI: 1.1–4.9; $p = 0.01$, and uninfected women: aOR: 2.3; 95% CI: 1.2–4.4; $p = 0.03$).

Otherwise, the profile of women reporting intimate partner sexual violence differed according to HIV serological status. HIV-uninfected women reporting having partners maintaining concurrent relationships out of household were more likely to report intimate partner sexual violence (aOR: 2.4; 95% CI: 1.1–4.9; $p = 0.02$). For HIV-infected women, intimate partner sexual violence was associated with reporting suicidal thoughts (aOR: 1.9; 95% CI: 1.2–3.4; $p = 0.01$), having partners who were involved in fights and/or riots with other men (aOR: 2.6; 95% CI: 1.2–5.5; $p = 0.01$), and reporting a higher submission index (aOR: 1.6; 95% CI: 1.2–2.0; $p < 0.001$).

Discussion

We reported here on the prevalence of lifetime intimate partner physical and sexual violence according to HIV status among women recruited in health facilities in Togo. Our main finding is that the prevalence rates of both lifetime physical and sexual violence in 2011 were very high among HIV-uninfected women and even higher among HIV-infected women in this West African country. The prevalence rates we documented among uninfected women are similar to those estimated using the same methodology within population-based surveys from East Africa, both in terms of physical violence (32–49%) and sexual violence (23–58%) (4). On the contrary, more than half (63.1%) of the HIV-infected women in Togo reported lifetime intimate partner physical violence, which is almost twice as high than among uninfected women interviewed (39.3%) and much higher than the rates observed among HIV-infected women in Nigeria (6%) (21), or in eastern Africa (17%) (22). In terms of lifetime intimate partner sexual violence, the prevalence rate we documented among HIV-infected women in Togo (69.7%) is twice the rate of that among uninfected women and considerably higher than among other reported estimations in Africa, such as in Uganda (12%) (22). We reported here as well that more than half (51.6%) of the HIV-infected women had been victims of both types of violence, while this proportion was 18.6% among uninfected women.

Bruises were overall the most frequent injuries reported among African women victims of physical violence (23), but the proportion of Togolese women reporting serious and disabling injuries such as dislocations (62.9%) and deep cuts (28.9%) is alarming. The severity of the consequences of intimate partner violence is often underestimated. Indeed, in our study, a substantial proportion of women reported needing medical care after being severely injured, but only a few actually accessed medical care and, if they did, they rarely disclosed the real causes of their injuries. Finally, none of the injured women in our sample had been referred to existing organizations providing psychological support. These findings suggest that case detection of intimate partner violence should be systematically done by medical staff, and particularly

Table 4. Factors associated with intimate partner physical violence according to their HIV status: Lomé, Togo, May–July 2011

	HIV uninfected						HIV infected					
	OR	95% CI	*p*	aOR	95% CI	*p*	OR	95% CI	*p*	aOR	95% CI	*p*
Women's sociodemographic profile												
Age												
>33 y/o	1			1			1					
<33 y/o	2.02	0.99–4.09	0.05	0.39	0.17–0.88	0.02	0.93	0.58–1.50	0.78			
Education												
Not instructed	1						1			1		
At least primary level	1.58	0.38–6.58	0.53				1.99	0.99–3.99	0.05	2.05	1.00–4.19	0.05
Contraceptive methods[a]												
Yes	1			1			1					
No	1.65	0.83–3.27	0.15	2.28	1.03–5.01	0.04	1.05	0.65–1.68	0.84			
Modalities of entry to sexual life												
Age of first sexual intercourse												
>18 y/o	1			1			1					
<18 y/o	0.45	0.22–0.89	0.02	0.48	0.21–1.03	0.06	0.77	0.47–1.24	0.28			
Conditions of first sexual intercourse												
Consented	1			1			1					
Coerced	2.67	1.16–6.10	0.02	2.65	1.06–6.58	0.04	1.74	1.02–2.95	0.04			
Mental health												
Loss of interest[b]												
No	1						1					
Yes	1.07	0.52–2.16	0.86				2.90	1.71–4.91	<0.0001			
Suicidal thoughts[c]												
No	1						1					
Yes	1.53	0.72–3.27	0.27				1.75	1.09–2.80	0.02			
Suicidal attempts[c]												
No	1						1			1		
Yes	2.72	0.62–11.82	0.18				4.22	1.22–14.54	0.02	4.53	1.29–15.91	0.02
Partners profile												
Polygamous												
No	1						1					
Yes	1.86	0.70–4.89	0.21				1.48	0.92–2.37	0.1			
Concurrent relationships												
No	1			1			1			1		
Yes	2.86	1.42–5.73	0	2.51	1.13–5.52	0.02	2.37	1.45–3.88	0	2.21	1.33–3.65	<0.001

Table 4 (*Continued*)

	HIV uninfected						HIV infected					
	OR	95% CI	*p*	aOR	95% CI	*p*	OR	95% CI	*p*	aOR	95% CI	*p*
Alcohol consumption												
Never/occasionally	1			1			1					
Frequently	2.08	1.06–4.05	0.03	1.74	0.81–3.71	0.15	1.68	1.04–2.69	0.03			
Involved in fights/riots												
No	1						1					
Yes	4.6	1.16–18.12	0.03				2.06	1.10–3.82	0.02			
History of non-partner violence												
Physical violence after 15 y/o												
No	1						1			1		
Yes	0.93	0.47–1.82	0.84				1.51	0.93–2.46	0.09	1.54	0.92–2.56	0.1
Sexual violence after 15 y/o[d]												
Yes							1					
No							1.58	0.41–6.07	0.51			
Sexual violence before 15 y/o												
No	1						1					
Yes	8.33	0.94–73.22	0.06				1.7	0.81–3.54	0.16			
Financial autonomy												
Employment												
No	1						1					
Yes	0.64	0.31–1.28	0.21				0.93	0.51–1.66	0.8			
Financial autonomy to support herself[e]												
No	1						1					
Yes	0.77	0.39–1.51	0.45				0.92	0.57–1.47	0.74			
Submission index												
	1.18	0.89–1.53	0.24	1.33	0.97–1.80	0.07	1.13	0.91–1.39	0.28			

[a]Use of any contraceptive method at the moment of the survey.
[b]During at least two weeks for the last 12 months.
[c]At least once during last 12 months.
[d]Not enough subjects for the analysis among uninfected women.
[e]Having a financial autonomy to support herself and household without her partner for at least 1 month.

Table 5. Factors associated with intimate partner sexual violence according to their HIV status: Lomé, Togo, May–July 2011

	HIV-uninfected						HIV-infected					
	OR	95% CI	*p*	aOR	95% CI	*p*	OR	95% CI	*p*	aOR	95% CI	*p*
Women's sociodemographic profile												
Age												
>33 y/o	1						1					
<33 y/o	0.93	0.46–1.86	0.84				0.68	0.41–1.11	0.13			
Education												
Not instructed	1						1					
At least primary level	1.1	0.25–4.81	0.9				1.41	0.69–2.86	0.34			
Contraceptive methods[a]												
Yes	1						1					
No	0.7	0.34–1.43	0.33				1.23	0.75–2.01	0.41			
Modalities of entry to sexual life												
Age of first sexual intercourse												
>18 y/o	1			1			1			1		
<18 y/o	2.84	1.37–5.89	0.01	2.31	1.08–4.92	0.03	1.78	1.08–2.93	0.02	2.28	1.19–4.37	0.01
Conditions of first sexual intercourse												
Consented	1			1			1					
Coerced	2.34	1.02–5.33	0.04	2.18	0.92–5.18	0.08	2.87	1.54–5.34	<0.001			
Mental health												
Loss of interest[b]												
No	1						1					
Yes	1.93	0.89–4.14	0.09				7.51	4.26–13.24	<0.001			
Suicidal thoughts[c]												
No	1						1			1		
Yes	1.67	0.77–3.57	0.19				2.21	1.33–3.64	0	1.98	1.16–3.38	0.01
Suicidal attempts[c]												
No	1						1					
Yes	1.9	0.45–7.91	0.38				3.09	0.89–10.66	0.07			
Partners profile												
Polygamous												
No	1						1					
Yes	1.08	0.39–2.92	0.88				1.54	0.93–2.53	0.09			
Concurrent relationships												
No	1			1			1					
Yes	2.63	1.30–5.30	0.01	2.38	1.14–4.94	0.02	2.67	1.60–4.44	<0.001			

Table 5 (*Continued*)

	HIV-uninfected						HIV-infected					
	OR	95% CI	*p*	aOR	95% CI	*p*	OR	95% CI	*p*	aOR	95% CI	*p*
Alcohol consumption												
Never/occasionally	1						1					
Frequently	0.7	0.35–1.38	0.31				1.58	0.96–2.59	0.07			
Involved in fights/riots												
No	1						1			1		
Yes	2.35	0.68–8.09	0.18				2.87	1.39–5.93	<0.001	2.6	1.23–5.51	0.01
History of non-partner violence												
Physical violence after 15 y/o												
No	1						1					
Yes	0.46	0.22–0.93	0.03				2.84	1.70–4.72	<0.001			
Sexual violence after 15 y/o[d]												
Yes							1					
No							4.51	0.56–35.71	0.15			
Sexual violence before 15 y/o												
No	1						1					
Yes	3.88	0.68–21.91	0.13				2.83	1.14–6.99	0.02			
Financial autonomy[e]												
Employment												
No	1						1					
Yes	0.64	0.31–1.29	0.21				1.35	0.74–2.43	0.32			
Financial autonomy to support herself[a]												
No	1						1					
Yes	0.68	0.32–1.39	0.29				0.7	0.42–1.15	0.16			
Submission index												
	1.05	0.80–1.37	0.72				1.66	1.30–2.10	<0.001	1.58	1.23–2.03	<0.001

[a]Use of any contraceptive method at the moment of the survey.
[b]During at least two weeks for the last 12 months.
[c]At least once during last 12 months.
[d]Not enough subjects for the analysis among uninfected women.
[e]Having a financial autonomy to support herself and household without her partner for at least 1 month.

within HIV care services. Clinical care evaluation checklists could include items related to physical and sexual violence to actively detect intimate partner violence. In addition, to ensure adequate case management, medical staff should be sensitized about intimate partner violence and consequences management and should be able to refer women to the appropriate supporting structures.

Although the prevalence of physical and sexual violence varied according to the HIV status among women of our sample, we identified three associated factors that are common to both groups. Reported partner multiple concurrent relationships were associated with higher rates of physical and sexual intimate partner violence regardless of serological status. Other African studies have reported similar findings, whereby women whose partner had several female partners were more likely to report sexual intimate partner violence and women suspecting their partner's infidelity were at higher risk of any kind of violent act perpetrated by their male partner (12, 24–26). In Tanzania and South Africa, men acknowledging having multiple female partners confessed that being questioned about their fidelity could trigger physical and sexual violent acts against their female partner (27, 28). Gender norms in many African cultures expect masculine men to be in control of women, and this control can take the form of sexual multi-partnership and violent acts. On the other hand, the prevailing ideal of femininity in such contexts may prevent women from refusing these sociocultural patterns, and on the contrary seems to promote the acceptance of this behavior, increasing their risk of contracting HIV infection through sexual assaults (29). Multi-partnership, mostly among men, is an increasing HIV risk behavior in West African countries and the need to intensify behavior change efforts have been already pointed out (11). We believe that such efforts should focus on tackling masculinity construction, fostering women's respect, and reducing gender inequality, all of which should be part of a comprehensive HIV behavior change preventive package.

We observed that starting sexual life before 18 years old was very frequent and appeared to be a risk factor of intimate partner violence for all women, regardless of their serological status. The high proportion of HIV-infected women experiencing a first forced sexual intercourse in our study is consistent with findings in South Africa (30). Since sexual abuse most often means unprotected sexual intercourse, these women may have been at the same time exposed to the risk of contracting HIV infection since very early ages and led into the vicious cycle of intimate partner violence (31). Age-appropriate sexuality education contributes to more responsible sexual behavior; nevertheless, gaps in basic knowledge about HIV and its transmission among young men and women remain important challenges (11). Sexuality education should be considered as a gateway to prevent HIV infection through a change of traditional gender norms based on fostering responsible and respectful sexual behaviors as early as possible in life.

Finally, prevailing submissive attitudes among Togolese women, expressed by an overall high acceptance of partner controlling behaviors and high submission index score, were associated with intimate partner violence, principally among HIV-infected women. Many women fearing intimate partner violence, even when aware of an HIV risk, may feel powerless to discuss infidelity, condom use, and HIV testing with their male partner (31). Renewed efforts are needed to foster women empowerment, including negotiation skills for safe-sexual practices addressed to women victims of intimate partner violence.

Several limits to our study need to be acknowledged. First, intimate partner violence may be a very sensitive subject for women and data collection was based on past experiences. We thus should not rule out a potential recall bias. To reduce information bias, however, interviewers were trained before conducting the survey and interviews were carried out in a private office. Further, due to the cross-sectional design of our study, we were not able to demonstrate a causal link between HIV infection and intimate partner violence or to explore the dynamic among these factors; however, our findings may have confirmed some of the factors to target when aiming at preventing intimate partner violence within clinical care services. Moreover, we did not present data on intimate partner psychological violence, as this would have required a thorough psychological assessment that could not be performed at the time of the survey. Finally, our study was conducted among a specific population of women attending a hospital facility in Lomé, and having been tested for HIV at least once in their life; thus, our results are not representative of all women in Togo.

One of the main strengths of our study, however, is its contribution to the pool of data available on intimate partner violence, data that can be compared to other settings as it was based on the use of *WHO Multi-Country Study on Women's Health and Life Events* questionnaire. Our study highlights that intimate partner violence is a true public health issue in Togo, with a high social burden and severe health consequences on women, and especially among HIV-infected women. Our findings argue, in particular, for systematic case detecting of intimate partner violence – as well as any form of violence – within HIV services, to provide adequate medical care to women in need and to advise them about help-seeking strategies. Taking into account the high rate of HIV-discordant stable couples in sub-Saharan Africa, couple-oriented interventions are a priority among primary HIV preventive strategies (13), and because intimate partner violence, highly prevalent in West African contexts and one important consequence of HIV serological disclosure among HIV-infected women, is a major barrier to the

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acceptability of such approaches (12, 13), the assessment of intimate partner violence should be included in couple-oriented HIV preventive strategies.

Finally, tackling cultural representations and the social construction of masculinity and traditional gender norms in sub-Saharan African contexts is an important challenge to achieve behavior change in terms of sexual health and must be addressed from adolescent ages. Further longitudinal research is needed to understand HIV-serodiscordant couple dynamics with regard to intimate partner violence in African contexts and thus improve the acceptability and efficacy of couple-oriented HIV preventive interventions. Intimate partner violence, being highly prevalent in resource-constrained settings and a major public health concern, global health policies must turn more firmly to this issue.

Authors' Contribution

JBS wrote the statistical analysis plan, cleaned and analyzed the data, and drafted and revised this paper. JOG wrote the statistical analysis plan, analyzed and interpreted the data, and drafted and revised this paper. GE designed the data collection tools, monitored data collection, wrote the statistical analysis plan, analyzed and interpreted the data, and revised this paper. AW and BK designed the data collection tools, collected the data, monitored data collection, and revised this paper. AP and ALE designed the data collection tools, collected the data, and revised this paper. VL and FD interpreted the data and revised the paper. DKE designed the data collection tools, wrote the statistical analysis plan, interpreted the data, and revised this paper. RB designed the data collection tools, wrote the statistical analysis plan, analyzed and interpreted the data, and drafted and revised this paper; he is the guarantor.

Statements:

The study protocol was approved by the National Ethic Committee of the Ministry of Health of Togo. All participants provided written informed consent.

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Conflict of interest and funding

None of the authors has any conflict of interest to declare (as per the Unified Competing Interest form).

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9. Reproductive health of HIV-infected women of reproductive age in sub-Saharan Africa: a public health challenge.

9.1. Restoration of reproductive functions among HIV-infected individuals

The advent of antiretroviral therapies in resource-limited settings has considerably improved both the life expectancy and quality of life of people living with HIV and AIDS. The dramatic reduction of AIDS-related morbidity and mortality owed to the rapid roll-out of antiretroviral drugs in resources-limited settings has significantly contributed to the restoration of physical and social functions of HIV-infected individuals. Current literature suggests as well that this outstanding improvement of health status has also restored fertility functions among HIV-infected population, leading to a greater desire to bear children.

Although HIV diagnosis has been hypothesized to be associated with an increased desire to cease childbearing (179); after ART initiation, many HIV-infected individuals choose to have children (180, 181). However, for HIV-infected individuals, choosing to procreate and having children implies potential health life-threatening challenges, particularly for HIV-infected women (182).

For serodiscordant couples desiring to procreate, engaging in unprotected sexual intercourses could become a major health threat as they increase the risk of transmitting HIV to uninfected partner (182). Indeed, current epidemiologic estimations point out that serodiscordant couples play an important role in maintaining global HIV epidemic. According to epidemiologic surveys, it is not uncommon that HIV-infected individuals engage in serodiscordant couples in sub-Saharan Africa: in settings with concentrated epidemics 0 to 6% of all couples are serodiscordant, while in settings with generalized epidemics this proportion goes from 9 to 17% (183, 184). In high prevalence settings, more than half of HIV-infected individuals have an uninfected partner; in settings with lower prevalence rates, this proportion may be as high as 75%(184). Estimations of a mathematic models showed that 29% (10 – 52%) of all new HIV infections occurred in serodiscordant couples(185). Although

recent sounding scientific evidence point out the great benefit of antiretroviral treatment in preventing HIV transmission (41), serodiscordant couples contributes substantially to the overall burden of disease(183).

For HIV-concordant couples, unprotected sexual intercourses may represent an important health risk as well. It has been established that infections with more than one strain of HIV-1 – dual infection – do occur(182). The term dual infection refers to the acquisition of two separate viral strains during primary infection or well a superinfection, which is the acquisition of one or more different viral strains after sero-conversion(186). Superinfection might lead to the acquisition of drug-resistant strains (187, 188) and it has been associated with an accelerated disease progression (189, 190).

Importantly, for an HIV-infected woman, besides de potential risk of transmitting the virus to her child; becoming pregnant without the appropriate clinical management might lead to important risks for her own health as well. HIV infection is one leading cause of maternal mortality in resource-limited settings (24, 191). In addition, although pregnancy at ART initiation has not been associated with higher risk of impaired virological responses(192); it is suspected that pregnancy after ART initiation, increases modestly the relative and absolute risk of virologic failure(193). Indeed, for HIV-affected couples, choosing to procreate represents a major challenge, particularly in resource-limited settings.

In the light of these important health risks, the increasing will of childbearing observed among HIV-infected individuals coupled with the increasing rates of pregnancy, particularly post-ART initiation are subjects of major public health concern. The measure of procreation desires of HIV-infected individuals and the identification of its potential predicting factors are important inputs in order to design strategies aiming at correctly fulfill reproductive needs of people living with HIV, reducing simultaneously the potential risk of HIV transmission and, the pregnancy-related health risks for HIV-infected women(194). In addition, estimating the incidence rates of pregnancy following ART initiation might be very useful in order to design strategies of safe motherhood tailored to HIV-infected women of reproductive age.

Firstly, within this chapter, I will present an insight about current knowledge in terms of measure of procreation desires among HIV-infected individuals, particularly after ART initiation. This insight includes findings of studies aiming at measuring to what extent HIV-

infected individuals are willing to procreate and what factors are potentially influencing this decision among this population.

The second section of this chapter summarizes findings of different studies which have provided the measure of the incidence rate of pregnancy among HIV-infected women as primary or secondary outcome. This section will be listing and describing different factors associated to incidence rate of pregnancy as described in literature. Finally, to close this chapter, the second peer reviewed scientific article of this research framework will be presented. This article aimed at estimating incidence rate of pregnancy among HIV-infected women post-ART initiation within eight West-African countries.

9.2. Fertility intentions and desire of procreation among HIV-infected individuals

The second prong of the Global Plan of Elimination of New HIV infection among children and keeping their mothers alive aims at reducing the unmet needs of family planning to zero among women of reproductive age as a preventive strategy of mother to child transmission of HIV. To effectively narrow the gaps in terms of unfulfilled reproductive health needs, understanding the reproductive dynamics of individuals of reproductive age is one first step to achieve this goal, and this is particularly important in settings of high HIV prevalence and high fertility rates.

In addition, it has been hypothesized that a HIV positive diagnosis may influence reproductive decision making, changing probably the plans of procreation of affected individuals. These changes are suspected associated to their self-perception of health status and their knowledge in terms of HIV-related health risks associated with pregnancy and postpartum. However, with the advent of antiretroviral treatment, particularly in high HIV prevalence settings; the patterns in terms of child bearing desires among HIV-infected individuals are suspected to be changing.

In order to better understand reproductive behaviors and patterns among HIV-infected individuals the measure of the desires and intentions of procreation among this population is one first step. Estimating to what extent HIV-infected individuals are willing to procreate is one key first input to correctly design public health strategies aiming at integrating family planning services within HIV care. Moreover, understanding reproductive dynamics of HIV affected individuals will provide health care staff with key information about how address correctly reproductive health issues of this population.

Over the last decade, a growing body of scientific evidence estimating patterns and explaining trends of procreation desires among HIV-infected population has been published worldwide. In addition, these scientific assessments have also documented biological and psychosocial factors associated with the desires and intentions of childbearing among HIV-affected individuals. The aim of the following section is to present and discuss findings of current scientific evidence aiming at estimating procreation desires and intentions among

HIV-affected individuals and the associated biological and psychosocial factors to this outcome.

9.2.1. Fertility intentions among HIV-infected individuals in high-income settings: North America and Europe.

Studies conducted in North America and Europe pointed out that in average 30% of HIV-infected individuals reported a positive desire of having children in a near future. Findings of Chen et al within a cross-sectional study based in a national-size population sample of the United States, pointed out that 28% of HIV-positive heterosexual or bisexual HIV-infected men and 29% of HIV-positive women who receive medical care desired children in the future(195). Similar findings were reported by further studies conducted in the United States. Cross-sectional studies conducted among HIV-infected women in this same setting pointed out that the positive desire of procreation was present in more than 20% of the HIV-infected women interviewed(196, 197).

In contrast, the desire of childbearing among HIV infected women in Canada was somewhat more heterogeneous. Findings of Loufty et al. showed that 69% (95% CI, 64%-73%) of HIV-infected women in Ontario stated positively that they would like to give birth in the future and 57% (95% CI, 53%-62%) intended to give birth in the future (198). On the other hand, according to findings of Oglivie et al in this same setting the proportion of women indicating a positive intention to have children was of 26%.

Findings of European studies didn't differ sensibly of those of North America. In France, 33% of HIV-infected women and 20% of HIV-infected men reported expecting to have a child in the future(199). In Switzerland, the proportion of HIV-infected individuals reporting a positive desire of child bear was higher than in France. Findings of a cross-sectional study conducted within a Swiss cohort of HIV-infected individuals showed that 45% of women and 38% of men expressed a positive desire for children in the future(200).

9.2.2. Fertility intentions among HIV-infected individuals in low-and-middle-income settings of high prevalence rate of HIV: Sub-Saharan Africa.

In sub-Saharan Africa, the assessment of reproductive intentions among HIV-infected individuals started more recently than in high-income settings. The studies included in this review assess fertility intentions in two different ways: 1) Interviewing HIV-infected men and women individually, 2) interviewing HIV-affected couples whether they are serodiscordant or both HIV-infected.

A cross sectional study conducted within a sub-urban clinical care service by Oladapo et al in urban Nigeria showed that the proportion of HIV-infected individuals reporting a positive desire of childbearing was as high as 63%. Moreover, this study reported as well that 71.5% of men and 94% of women who desired procreate intended to have two or more children within a near future(201). Contrasting with former findings, a more recent study conducted in rural Nigeria showed that the proportion of HIV-infected individuals desiring a child within a near future was sensibly lower than in urban or peri-urban setting. Olowookere et al reported that 27% of women and 17% of men in rural Nigeria reported a positive desire to have more children in a near future (202).

Contrasting with West Africa, findings from East Africa appeared to be different. According to findings of Nakayiwa et al in Uganda, although 42% of participants of the study were sexually active and 33% were engaging in pregnancy risk behaviors, only 18% expressed a positive desire of having children(203). Consistently with these findings, a larger study conducted among Ugandan HIV-infected men and women showed that 14% of all participants wanted to have more children (180). In Tanzania, although more than half of HIV-infected individuals reported being actively engaged in unprotected sexual practices, the positive desire for a child or additional child, was expressed only by 37% of all participants (40% of males and 36% of females)(204).

Later on, findings of a study conducted by Myers et al in South Africa revealed that the desire of child bearing among HIV-infected individuals was sensibly different. Indeed, this cross-sectional study aiming at estimating the prevalence and determinants of fertility intentions of HIV-infected women and men receiving antiretroviral therapy in rural South

Africa pointed out that only 29% of the interviewed individuals stated that they wanted to have children in the future. Furthermore, in this study the proportion of men reporting a positive desire of childbearing was slightly higher than the proportion of women (36% versus 26%)(205). In contrast, findings of Cooper et al showed that the proportion of HIV-infected individuals on ART reporting a positive desire of childbearing was slightly higher in urban Cape Town, South Africa. Indeed, in this cross-sectional study conducted in urban clinical care setting, 57% men and 45% of HIV-infected women reported being open to the possibility of having a child(181).

9.2.3. Fertility intentions among HIV-affected couples in low-and-middle-income settings of high prevalence rate of HIV: Sub-Saharan Africa.

As in sub-Saharan Africa an important number of HIV-infected individuals reported being in couple, the desire of childbearing is maybe influenced by this fact, and several studies have therefore estimated this outcome among HIV-affected couples. Beyeza-Kashesya J et al estimate the proportion of positives intentions of childbearing among HIV-affected sero-disclosed couples in Uganda. Findings of this study showed that more than a half (59%) desired to have children in the future(206). A larger study exploring the same question and comparing HIV-infected couples with uninfected peers found out that HIV positive individuals were more likely to want no more children compared to their HIV negative peers (with adjusted odds ratios of 4.9 (95% CI 2.7–8.9) for men and 7.4 (95% CI 3.2–16.7) for women)(179). Moreover, findings of this study showed as well that the desire of stop childbearing was higher among concordant HIV-positive couples 27/38 (71%) and lowest among concordant HIV-negative couples 325/1260 (26%)(179).

Findings of a similar study conducted in Kenya and Uganda investigating fertility intentions among serodiscordant couples were not so different. In Kenya and Uganda 36% of HIV-infected women and 28% of HIV-infected men reported a positive will of childbearing. For the majority of couples (76%), HIV uninfected partners were in agreement with the fertility intentions of their HIV infected partners: for 314 couples (55%), both members did not want more children, whereas for 121 couples (21%), both members desired additional children. One hundred thirty-six couples (24%) had discordant fertility intentions, the majority of

which (74%) were couples in which the HIV-1 uninfected male partner desired additional children but their HIV-1 infected female partner did not(207).

9.3. Predictors of the positive desire of procreation among HIV-infected individuals

According to findings of the studies included in this literature review the factors defining the will of childbearing among HIV-infected men and women can be grouped in the following categories: Biologic factors, psychosocial factors and HIV-related clinical factors.

9.3.1. Biological factors associated with the desire of procreation among people living with HIV.

Biological age is one major factor found almost systematically significantly associated with the positive desire of childbearing (180, 201-203, 205, 208). Unsurprisingly, fertility intentions decreased proportionally to biological age, particularly for women. Therefore, older women (>35 years old) were almost systematically less likely to report a positive desire of childbearing. For example, in Nigeria, women between 15 and 34 years old are almost 3 times (aOR: 2.94; 95%IC: 1.31 – 6.64) more likely to report a positive desire of childbearing than their older counterparts (202).

One biological factor associated with HIV-infection hypothesized associated with childbearing desires among HIV-infected individuals is the knowledge of HIV serological status. Findings of Dube et al in Malawi pointed out that the knowledge of HIV positive status is associated with an increased reported desire to cease childbearing(179). Findings of Dube et al, also underscored the fact that although the awareness of an HIV positive status reduce de desire of childbearing, among the study population the proportion of HIV-infected individuals using any contraceptive methods was very low in this setting(179).

In addition, a study conducted in Uganda among women of reproductive age attending to antenatal clinics regardless their serological status showed similar findings. Within this study all women attending to antenatal clinics were surveyed on their fertility intentions and received an anonymous HIV test. HIV-positive women reported a lower fertility intentions than their HIV-negative counterparts [age-adjusted RF = 0.83, 95% confidence interval (CI): 0.75–0.93](208).

A second important factor hypothesized associated with reported childbearing desires is antiretroviral treatment. It has been suggested that, besides the known effect of ART on restoring health status of HIV-infected individuals, it may indirectly increase the childbearing desires through the improvement of their perceived health. Findings of Kipp et al in Uganda, showed that although HIV-infected individuals were more likely to want more children than their counterparts not yet treated, this difference was not statistically significant (18.2% on HAART vs. 10.7% not on HAART, p = 0.131)(180). Conversely, according to findings of Cooper et al in South African, being on ART is a determinant of positive desire of childbearing, particularly for women(181). The odds of intending to have a child in the near future, increased significantly among HIV-infected women on ART compared to those not yet on treatment (aOR: 2.41; 95%IC: 1.28–4.54).

Moreover, although it has been suggested that fertility intentions and desires of having a child might varies over time since a positive diagnosis, within this review only one longitudinal study aiming at analyzing the trends of the desire for children over the time among HIV-infected women of reproductive age.

This study conducted by Homsy et al among a cohort of 711 HIV-infected Ugandan women of reproductive age initiating ART, accounting for 2.4 years of follow-up and showed that fertility desires changes significantly over the time for HIV-infected women.

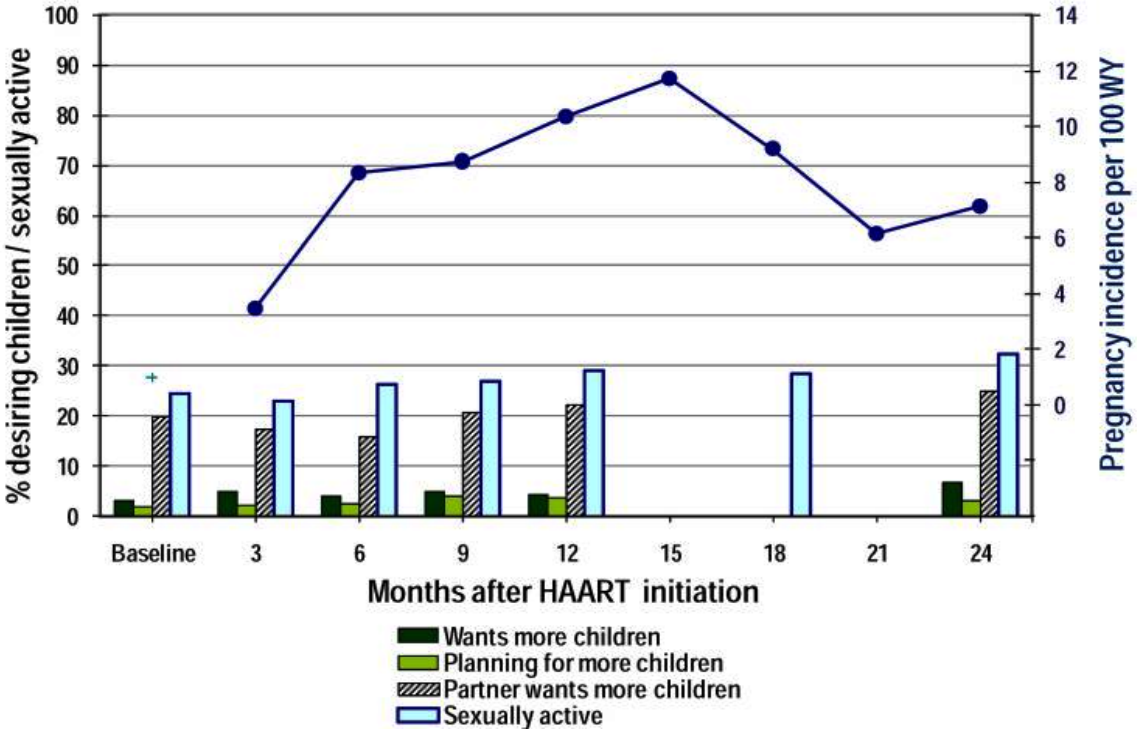

Figure 20. Desire for children and incidence of pregnancy among HBAC women on ART.

As shown in figure 20, the desire for children increased significantly over follow-up for both women (p<0.004) and their partners (P=0.0001), but remained under 7% for the women and under 26% for their partners throughout follow-up(209)

9.3.2. Psycho-social factors associated with the desire of procreation among people living with HIV

In the literature an important number of psycho-social and cultural factors have been identified as predictors of the desire of procreation and fertility intentions among people living with HIV in sub-Saharan Africa. There are individual factors, factors associated with couple dynamics and factors more related to health providers. The following section presents several of them, explaining in part the mechanism of their association with the desire of procreation.

Several studies point out that men are often reporting higher desires of child bear than women (180, 181, 205, 207, 210). It is suspected that this increased male desire of child bear obeys to cultural and social gender norms (211, 212). According to qualitative research, the drivers of fertility desires may also differ according to gender perceptions of men and women and this is regardless serological status.

In many cultures, having children is a major requirement for both men and women identity(212). Assuring the continuity of the lineage and their kin is men responsibility and a major masculine driver of reproductive decision (210, 212). In addition, men possessing knowledge of benefits of antiretroviral treatment on preventing mother–to-child transmission were more favorable towards having children in the future, this is regardless their knowledge on availability of these treatments in their setting (213, 214). Differently, for women the knowledge of the existence of PMTCT does not influence their fertility intentions unless they are sure about availability of ART, pointing out the fact that preventing children's infection is as important as maintaining their own health in order to subsequently be able to take care of children(213-215)

Although HIV-infected women are more concerned about the potential repercussions of pregnancy on their own health, the future of the orphaned children, motherhood grants them an identity and respect in the African societies(212, 216).

Thus men and women would rather prefer to face risks of HIV transmission to their partners or their children than be tagged as infertile, in order to fit within African gender norms(212).

9.3.2.1. Reproductive decisions within couple dynamics

Firstly, for HIV-infected men and women, having a current partner within a former relationship is associated with a positive desire of childbearing regardless partner's serological status (203, 205). In addition, it appeared that for HIV-infected women, being in a relationship for at least five years increased significantly the odds of desiring to child bear (205, 207). Among African HIV-infected women, marriage has been identified as a potential predictor of future intentions of childbearing (181, 202). Frequently, some women's desires of not having children is strongly outweighed by partner and family expectations or societal norms regarding fertility and family formation (213, 216). In many African societies, motherhood is considered a major social and cultural defining feature of women's adult live (217, 218).

For married women or those intending marriage, exercising their right of choosing not to procreate is very difficult regardless of their HIV status. Conversely, family and societal expectations exert less pressure on men regarding parenthood (212, 213, 216). These differences emphasize the gender power imbalances in intimate relationships between men and women and the less powerful position occupied by women in the society (212, 213)

However, findings of qualitative assessments conducted among HIV-affected couples point out that child bear under a HIV-positive diagnosis becomes an important dilemma, particularly for serodiscordant couples(219). Among the most common challenges reported by serodiscordant couples willing to procreate findings underscored: 1) Dealing with the emotional and sexual impact of HIV on the relationship and the fear of transmitting the infection to partner and child; 2) disclosing serological status to partner, family and friends; 3) confronting reproductive decisions and the lack of negotiating power for safer sex of uninfected partner (this happen more often among female partners); 4) The limited capacity of health system in offering safe methods of reproduction and (219, 220).

In order to avoid HIV-related stigma, women who had not disclosed their status are pressured to have children to avoid raising community suspicions regarding their HIV status(213). However, for women and men who had already disclosed their status, seeking

to have children is socially unacceptable(221). The expressed desire of child bearing among HIV-affected couples is highly stigmatized. These attitudes exert an important pressure on women, and become a major constraint to disclose their HIV positive status(213)

Secondly, according to several studies, having few or not having children with current partner is a third important factor associated with a positive desire to procreate (181, 201, 204, 205). The desire for procreation decreases significantly with the number of living children for HIV-infected women and men (181). This decrease is slightly more important when the living children were conceived within the current couple (204). For several childless men and women, living with HIV strengthened their desire for children through the fact that having a child give them “hope and happiness” and brings somehow “normality” to their lives(213). For some serodiscordant disclosed couples the desire of a child goes beyond their perception of risk of acquiring HIV infection (206, 219, 222). Findings of Beyeza-Kasheya et al in Uganda revealed that for some negative partners engaging in serodiscordant relationships, the desire of procreation is so strong that they are ready to risk acquiring HIV infection at the expense of getting children(219).

However this attitude seems to change when individuals have already experience the loss of a child to AIDS. Although the desire to have another child to replace one they had lost already is present in a few individuals, according to cooper et al, the predominant effect was to deter women and men from further childbearing(213).

9.3.2.2. Health care workers attitudes towards childbearing

The attitudes of Health care providers towards childbearing desires exert an important influence on reproductive decisions of HIV-infected individuals. Although women are encouraged to discuss their procreation plans with health care providers, an open discussion on this subject is often a great source of anxiety, particularly for HIV-infected women. Fears of facing judgmental attitudes regarding their reproductive options seems to be a major hurdle for HIV-infected women to start an open discussion with health care providers about reproductive intentions (213, 219).

Despite that health care workers seem open to discussions of pregnancy plans, scientific evidence suggests that their attitudes are often unsupportive and disapproving, dissuading HIV-infected women who express a positive desire of becoming pregnant to stop

childbearing (213, 215). This conflicting result may be explained by the expectations in terms of their professional role of guiding women's reproductive choices, while at the same time they are confronted to their own fears around the future of the baby and the mother(215). Clients who discuss with health care provides about their reproductive decisions and future desires of child bear were three times more likely to use condoms consistently(215). The attitudes of health care providers towards ceasing childbearing after an HIV positive diagnosis are understood as a preventive message in order to reduce the risk of transmitting or acquiring HIV infection and reducing the number of HIV orphans(215).

9.2. Incidence of pregnancy among HIV-infected women on ART

9.2.1. Epidemiological trends of incidence rate of pregnancy following ART initiation

As seen before, a positive diagnosis of HIV might modify but it does not eliminate the broader desire of childbearing among HIV-infected adults. Owed to the reduced life expectancy of HIV-infected women before ART era, pregnancy was not a very common event after a positive diagnosis of HIV. The rapid progression of untreated HIV disease threatened reproductive functions of HIV-infected women, reducing considerably the probability of becoming pregnant.

Notwithstanding, scientific evidence analyzed in the previous chapter suggest that the introduction of antiretroviral treatment have had an important influence in reproductive decisions of HIV-infected individuals. Indeed, the outstanding improvement of health status and self-health perception provided by antiretroviral treatment has made HIV-infected individuals reconsider the possibility of childbearing.

Besides the expressed growing desire of procreation, the increasing rates of pregnancy after initiating antiretroviral treatment corroborate this statement. Current estimations point out that with the advent of antiretroviral treatment, pregnancy became a more frequent event among HIV-infected women, suggesting a more biologic hypothesis explaining the effect of antiretroviral drugs on reproductive functions. This hypothesis set out that besides the recognized benefit of antiretroviral treatment on restoring health status of HIV-infected individuals; these drugs may also have a positive effect on the biology of reproductive functions. In order to better understand to what extent existing scientific evidence underpin this hypothesis we explored the estimations of the incidence rate of pregnancy among African HIV-infected women on antiretroviral treatment.

Pregnancy is a well-known transmission path of HIV infection from HIV-infected mothers to their child. Moreover, pregnancy is a reliable indicator of unprotected sexual intercourses which may lead to an increased risk of HIV infection. Thus, I believe that characterizing the epidemiology of reproduction among HIV infected population, estimating incidence rates of pregnancy and its determinants, is one major priority in terms of public health. This information would help stakeholders in designing evidence-based strategies to correctly address reproductive needs of HIV-infected population.

In these regards, I conducted a literature review aiming at compiling existing epidemiologic scientific research studies estimating incidence rates of pregnancy among HIV-infected women. These estimations could have been reported as a primary outcome or as an additional secondary outcome of these studies. Within this literature review, I also looked at the factors associated with the incidence rate of pregnancy, the direction and the significance of their association. Only studies conducted in sub-Saharan Africa and published after the year 2000 were retained within this literature review.

9.2.2. Incidence of pregnancy among HIV-infected women in sub-Saharan Africa

Sixteen studies meeting inclusion criteria were retained within this literature review (table 1 and table 2). In Burkina Faso, Nebie, Y. et al estimated an incidence rate of pregnancy which was of 12.3 pregnancies per 100/women-year and Desgées-du Lou, A. et al in Côte d'Ivoire estimated 16.5 pregnancies per 100/women-years(223, 224). Although lower than former estimations, Bussman et al found in Botswana an incidence rate of pregnancy of 7.9 per 100 women-year (225).

Later in time, observational cohort studies started to produce this epidemiological indicator and incidence rates of pregnancy varied importantly. Indeed, estimations of incidence rates of pregnancy among HIV-infected women after ART initiation varied between 5.2 pregnancies per 100 women-years to 24.6 pregnancies per 100 women-years. Westreich et al, estimated incidence rate of pregnancy within an observational clinical cohort of patients on antiretroviral treatment in South-Africa and findings showed an incidence rate of pregnancy of 5.2 pregnancies per 100 women-years (95%IC: 4.8 - 5.5)(226). Estimations of incidence rate of pregnancy of studies conducted on similar contexts and under comparable methodological designs were very similar (209, 227-230).

On the other hand, findings of cohort studies axed on reproductive health outcomes showed higher incidence rates of pregnancy. A study conducted by Heffron et al in four Eastern-Africa countries (Zambia, Kenya, Rwanda, Tanzania and Uganda) using data from Partners in Prevention HSV/HIV Transmission Study, a randomized, placebo-controlled, HIV-1 prevention trial of daily acyclovir for herpes simplex virus Type 2 (HSV-2) suppression provided to HIV-1/HSV-2 dually infected members within heterosexual HIV-1 serodiscordant

couples found out an incidence rate of pregnancy among HIV-infected women on ART of 16.3 pregnancies per 100 women-year (95%CI: 14.9-17.7)(231). Although slightly lower, estimations of incidence rates of pregnancy post-ART initiation in other studies conducted in Malawi found out similar incidence rates. Hoffman et al and Taulo et al estimated an incident rate of pregnancy among HIV-infected women of 14.5 pregnancies per 100 woman-years and 13.9 per 100 woman-years respectively within a prospective cohort studies both conducted in Malawi (232, 233).

Finally, high incidences rates of pregnancy were reported by two studies, one conducted in South-Africa and the other in Uganda. In South-Africa, within a cohort study aiming at measuring fertility intentions and reproductive outcomes among HIV-infected women; Schwartz et al estimate an incidence rate of pregnancy of 21.6 pregnancies per 100 women-years (95%CI: 18.5-25.2) following ART initiation (234). Similarly, within an observational cohort of HIV-infected individuals on ART follow-up in Uganda the incidence rate of pregnancy as high as 24.6 pregnancies per 100 women-years (95%CI 18.1, 32.6) (235).

Table 1. List of research studies reviewed estimating the incidence rate of pregnancy among HIV-infected women.

Author	Setting	Type of study	crude incidence rate of pregnancy	incidence rate at last year of follow-up
Nebie et al, 2001	Burkina Faso	Prospective cohort of women on ART	12.3 pregnancies per 100 person-years	1st year: 4 per 100 person-years 3rd year: 18 per 100 person-years
Hoffman et al, 2008	Malawi	Prospective cohort of HIV-infected women	14.5 per 100 women-years	N/A
Taulo et al, 2009	Malawi	Prospective cohort of HIV-infected and uninfected women	Overall estimated pregnancy rate: 14.9 per 100 person-years (95% CI: 13.0–16.8). Pregnancy rates HIV infected: 13.9 per 100 person-years uninfected: 14.2 per 100 person-years (P = 0.94).	N/A
Heffron et al, 2010	South Africa - Zambia, Kenya, Rwanda, Tanzania, Uganda	Randomized Control Trial Partners in Prevention HSV/HIV Transmission Study. Prospective cohort of HIV-infected and uninfected women in heterosexual serodiscordant couples	HIV-infected incidence rate of pregnancy: 16.3 per 100 women-years (95% CI, 14.9-17.7) HIV uninfected: 15.6 (95% CI, 13.6-17.6) per 100 person-years	N/A
Desgrées du loup et al, 2002	Côte d'Ivoire	Randomized Control Trial ANRS 049 DITRAME	16.5 per 100 women-years	N/R
Schwartz et al, 2012	South Africa	Prospective cohort of HIV-infected women on ART	21.6 per 100 women-years (95%IC: 18.5-25.2)	**cumulative incidence of pregnancy** 1st year 23.9 per 100 women-year [95% CI 16.4–34.1] 2nd year 15.9 per 100 women-year [95% CI 12.0–20.8] >2 years 21.0 per 100 women-year [16.8–26.1]
Makumbi et al, 2011	Uganda	Observational cohort of HIV-infected women pre-ART and on ART	pre-ART: 13.1 per 100 women-year (95%IC: 10.14 - 16.75) post-ART: 24.6 per 100 women-year (95%IC: 18.1, 32.6)	The cumulative probability of incident pregnancy increased overtime and was higher among women with CD4 count ≥100+ compared to those with CD4 counts level of less than 100 cells/mm^3, but this difference was not statistically significant (log rank $\chi^2 = 2.32$; $p = 0.3133$).
Karim et al, 2011	South Africa	Prospective cohort of HIV-infected women	16.6 per 100 women-years (rural) 22.4 per 100 women-years(urban)	N/R

Table 2. List of research studies reviewed estimating the incidence rate of pregnancy among HIV-infected women.

Author	Setting	Type of study	crude incidence rate of pregnancy	incidence rate at last year of follow-up on ART
Gibb et al, 2012	Uganda/Zimbabwe	RCT	4.4/100 woman-years [95% CI 4.0-4.9]	N/R
Westreich et al., 2012	South Africa	Observational cohort	5.2 per 100 women-years. [95%IC: 4.8, 5.5]	Cumulative incidence of first pregnancy by six years 22.9 per 100 women-year(95% CL 20.6%, 25.4%).
Myer et al, 2010	Multicountry (Sub-Saharan Africa)	Observational cohort	Overall rate of pregnancy 7.7 per 100 women-years. **Pre-ART rate of pregnancy:** 6.51 per 100 women-years; (95% CI 5.73–7.38) **Post-ART rate of pregnancy:** 9.03 per 100 women-years; (95% CI 8.13–10.03)	**Cumulative incidence:** 1st year: 6.8 per 100 women-year 2nd year: 9.9 per 100 women-year 3rd year: 10.5 per 100 women-year 4th year: 13.7 per 100 women-year
Bussman et al, 2007	Botswana	Prospective cohort of women on ART	7.9 per 100 person-years	N/R
Homsy et al, 2009	Uganda	Prospective cohort of women on ART	8.2 per 100 women-years	**Cumulative incidence:** 1st quarter of time of follow-up: 3.5 per 100 women-year 5th quarter of time of follow-up: 11.7 per 100 women-year
Tweya et al, 2012	Malawi	Retrospective cohort study	9.3 per 100 women-years	**cumulative incidence:** 6 months: 2% (95% CI 1.31–2.19) 12 months: 7% (95% CI 5.89–7.66) 24 months: 17% (95% 15.64–18.67) 36 months: 25% (95% CI 23.69–27.97)
Kaida et al, 2013	Uganda	Prospective cohort of HIV-positive individuals initiating ART Uganda AIDS Rural Treatment Outcomes (UARTO)	9.4 per 100 women-years (95% CI: 7.68, 11.4)	Incidence of first pregnancy peaked between 6–12 months after ART initiation (15.2 pregnancies per 100 WYS (95% CI: 9.53, 23.0), declined and stabilized between 12–36 months, then decreased sharply 36 months after ART initiation.
Guthrie et al, 2011	Kenya	Prospective cohort of women on serodiscordant couples	10.0 per 100 women-years	**Cumulative incidence for women reporting a positive desire of procreation:** - 6-month cumulative incidence of 10.4% (95% CI, 6.9–15.6%) - 1-year incidence of 17.4% (95% CI, 12.5–24.0%) **Cumulative incidence for women not reporting a positive desire of procreation:** - 6-month incidence of 2.1% (95% CI, 0.9–5.0%) - 1-year incidence of 3.7% (95% CI, 1.9–7.4%)

9.2.3. Predicting factors of pregnancy incidence among HIV-infected women

9.2.3.1. Association of antiretroviral treatment with the incidence of pregnancy

It has been hypothesized that antiretroviral treatment may has an effect on fertility functions and several studies have addressed this issue comparing the incidence rates of pregnancy among women before and after ART initiation. In a multi-country cohort study conducted in seven sub-Saharan Africa countries, findings of Myers et al showed that the incidence rate of pregnancy was lower during the period prior to ART initiation, increasing significantly after ART initiation (6.5 per 100 women-years vs. 9.0 per 100 women-years)(227). As showed in figure 21, it appeared, that prior to ART, incidence rate of pregnancy was lower but also relatively constant, peaking discretely just before the third year on clinical follow-up. In contrast, following ART initiation, the risk of becoming pregnant increased proportionally to time on follow-up.

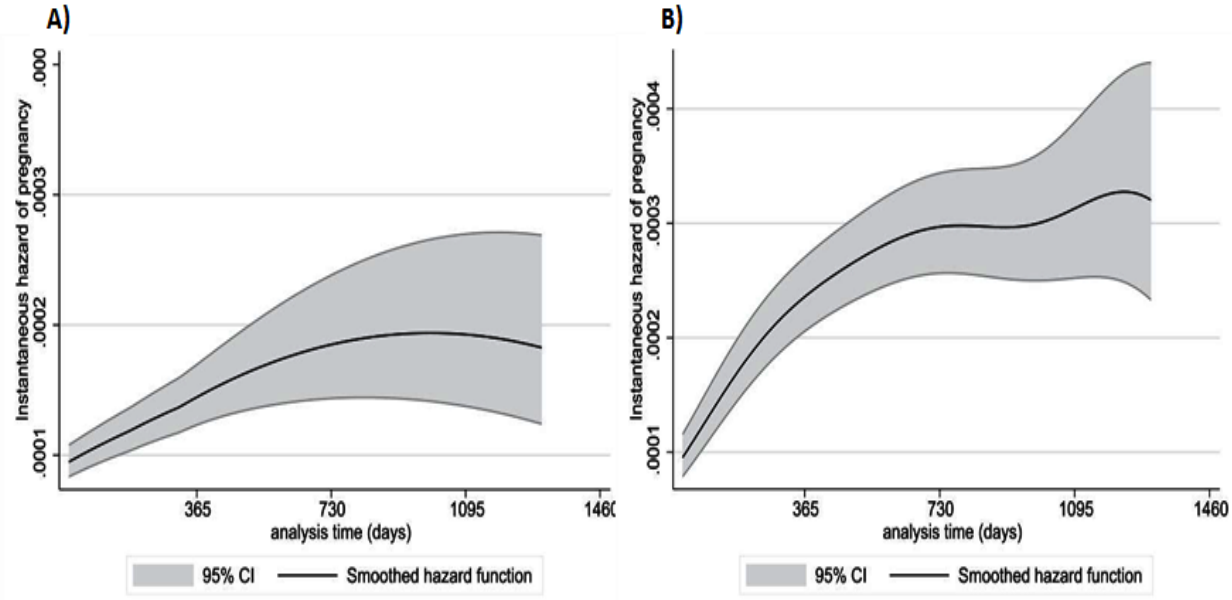

Figure 21. A) Instantaneous hazard of pregnancy during the pre-ART period by duration of follow-up, with 95% CIs.; B) Instantaneous hazard of pregnancy during the on-ART period by duration of follow-up, with 95% CIs. Source: Myers et al. PLoS Med, 2010.

Similarly, in Uganda, Makumbi et al have conducted a study aiming at comparing reproductive outcomes among HIV-infected women according to ART status. Findings of this study showed that incidence rate of pregnancy among women on ART was almost two times

higher (24.6 per 100 women-years) than among ART-naïve women on clinical follow-up (13.1 per 100 women-year)(235). To explain this differences Makumbi et al proposed a behavioral hypothesis which suggest that rapid and progressive improvement of health status and well-being favored by ART may increase hopefulness about the future and improve mental health. This improved health status may lead to a reevaluation of their intentions and decisions regarding childbearing; increasing sexual activity, particularly among women cohabiting in stable partnerships. However, whether or not the ART-related improvement of immunological functions, increases female fecundity and capacity to take pregnancy to term remains an unanswered question (227, 235).

In addition, one important epidemiological phenomenon observed is how the risk of becoming pregnant increases proportionally to time on ART. Indeed, it has been almost systematically documented by the studies estimating incidence rate of pregnancy after ART initiation within more than 12 months of clinical follow-up. The cumulative incidence rate estimated by several studies increase to more than 20% at 36 months comparing with around 2% during first year on ART follow-up (226, 228). Consistently with this increased cumulative incidence proportional to time on ART, other studies have suggested that the probability of becoming pregnant increases of roughly 30% after 36 months on ART follow-up(229). In the study conducted by Myer et al, crude incidence rate of pregnancy among HIV-infected women was of 13.7 per 100 women-years at year four of ART follow-up, more than two times higher than what it was during first year (6.8 per 100 women-years)(227).

Besides estimating the incidence rates and epidemiological trends of pregnancy, current scientific evidence has also documented associated factors of incident pregnancies among women on ART. Unsurprisingly, the most commonly cited are biological factors and chief among these is women biological age.

It seems that high incidence rates of pregnancy are more common among young women <35 years old. In addition, and consistently with this first finding, although incidence rate of pregnancy increases proportionally to time on ART, the probability of becoming pregnant decreases with women's biological age, peaking the higher rate among women of <25 years old. Westreich et al estimated a probability of 52.2% of becoming pregnant among women who started ART between 18-25 years old when compared to peers starting ART at older ages regardless their CD4 cell count at ART initiation (Figure 22) (226).

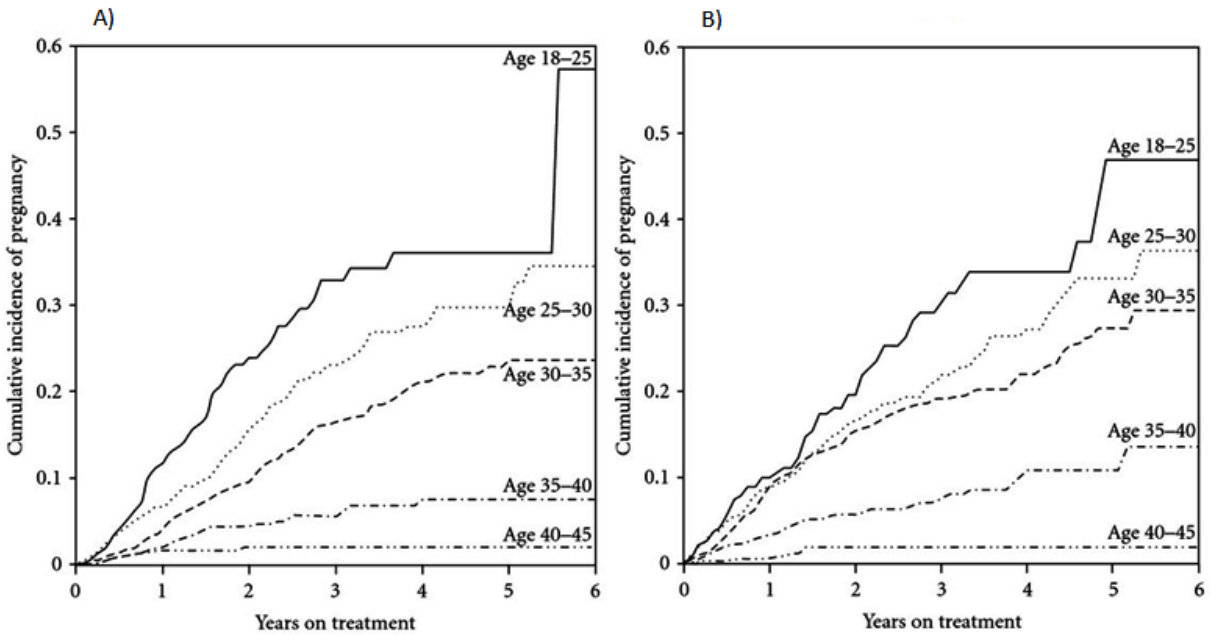

Figure 22. Cumulative incidence of first pregnancy among 5,996 women initiating HAART in Johannesburg, South Africa, from time of HAART initiation, by baseline age and baseline CD4 count: (a) ≤100 cells/mm3; (b) >100 cells/mm3.

One important associated factor increasing the risk of pregnancy among women on ART was the fact of having a current male partner. Although not statistically significant, being married or cohabiting with a male partner increased by 59% the risk of becoming pregnant after ART initiation (HR: 1.59; 95%IC: 0.94 – 2.69; p=0.08)(209). Additionally, if the HIV-infected women have disclosed her HIV status to current male partner the risk of becoming pregnant increased by more than two-folds (aHR: 2.45; 95%IC: 1.29 – 4.63) compared to those who haven't disclosed their serological status(229).

Other factors that found a statistically significant association with a higher risk of becoming pregnant were a high CD4 levels and WHO clinical stage. Women having higher levels of CD4 and during early clinical stages of AIDS disease according to WHO classification had an increased risk of becoming pregnant after ART initiation(227, 228). These last findings seems to be consistent with the biological hypothesis suggesting that even after an HIV positive diagnosis, healthier HIV-infected women are probably more up to become pregnant and take a pregnancy to term.

9.3. Discussion on fertility intentions and pregnancy incidence among HIV-infected African women on ART

9.3.1. Fertility intentions and desires

Findings of studies within the present literature review suggest that a positive diagnosis of HIV does not eliminate the future desire of child bear among HIV infected individuals. Moreover, findings suggest as well that the introduction of ART could probably have a positive influence on reproductive decision making of HIV-infected women and men. This particular finding might be corroborating with the hypothesis that the improvement of health perceived status favored by ART might influence positively reproductive decision making.

However, although studies suggest ART is a relevant factor increasing fertility desires among HIV-infected individuals, the same studies suggest that reproductive decisions among HIV-infected individuals could probably be predicted by an important number of other biological and psychosocial factors.

Biological age was found almost systematically associated with a positive desire of procreation. The desires of child bear decreased proportionally to women biological age. Younger women probably have not yet completed their reproductive goals, they are maybe more up to start or continue their procreation program, regardless of their serological status.

Moreover, besides biological age, it appeared that there are gender-related differences in terms of desires to bear a child. According to several studies, HIV-infected men were more likely to express a positive desire to have a child in the future than women of same serological status. HIV-infected women are probably more concerned about the potential repercussions of pregnancy on their health status and therefore more sceptics about becoming pregnant and bearing a child. On the other hand men are probably more focused in the gender norms which dictate that keeping the family kin is man duty.

In addition, for HIV-infected individuals the fact of being in couple is an important factor associated with a positive desire of child bear. Present findings point out that HIV-infected individuals in couple were more likely to express a positive desire of having children in the

future that their single counterparts. This finding suggests that couple dynamic may play a relevant role in terms of reproductive decision making.

Similarly, for those HIV-infected individuals in couple, disclosing HIV status appeared to be an important determinant of reproductive decisions. Although not systematic, for serodiscordant couples, disclosing serological status within the couple appeared to be associated with an increased desire to cease childbearing. Disclosing the serological status within the couple may probably increase the awareness about the risk of HIV transmission and the potential repercussions of pregnancy in women health status and making therefore the couple reconsider their will of child bear.

Moreover, among HIV-infected individuals engaging in couple relationships, the fact of having few or no child at all with current partner appeared to be significantly associated with a positive desire of childbearing. Within certain societies, parenthood grants men and women with an upgraded status, this is particularly true in African societies. Choosing not to child bear in African societies is often source of stigma, discrimination and exclusion thus HIV-infected individuals choose to procreate regardless the risk associated with their serological status.

Furthermore, the scientific evidence reviewed has explored as well the role of structural factors on reproductive decision making among HIV-infected individuals. According to findings, health care staff may play a relevant role on the way HIV-infected individuals make their reproductive choices. Current literature suggest that negative judgmental attitudes of health care staff about the HIV-infected individuals expressed will of child bear might influence their reproductive decisions, reducing the desires of child bear among this population. In one hand, judgmental attitudes of health care staff hinder effective communication on sexual and reproductive issues, becoming therefore probably a hurdle for an effective integration of sexual and reproductive programs within HIV care programs.

However, although these findings constitute an important amount of sounding scientific evidence describing and trying to explain reproductive decision making process among HIV-infected individuals, several methodological issues limit its interpretation. One major limit is the fact that the vast majority of these findings are outcomes of cross-sectional studies, and therefore causal and temporal relationships are difficult to stablish.

Fertility desires following a HIV positive diagnosis are suspected to experience important variations across time and cross-sectional designs are unable to capture the potentially changing pattern of these desires. Longitudinal designs are more appropriate to explain causality and capture changing patterns of procreation desires across the time. Among the reviewed studies, only one was conducted under a longitudinal prospective design(209).

Moreover, it is important to underscore the fact that desires and intentions of procreation are relative concepts but not exactly the same and therefore not necessarily measured by the same indicators. Several reviewed studies described clearly the outcome measure whereas this outcome was unclear in several others. In addition, it is worth to note that owed to the large variety of data collection tools used to capture the concepts of desire and intention of procreation among different studies, it is difficult to compare or extrapolate findings across the different settings.

Similarly, as the measure of fertility desires might be subject of sensitive personal information, information bias cannot be excluded. This bias could be related to the concept of social desirability as women answers are consistent with societal expectations from them as future mothers, regardless their knowledge on the repercussion on their health status.

According to findings of this literature review, the vast majority of studies aiming at measuring child bearing desires in sub-Saharan Africa have been mostly conducted in southern and eastern Africa. Besides two quantitative studies conducted in Nigeria and one qualitative study conducted in Côte d'Ivoire, data on this concern is scarce in West Africa. This fact may limit interpretation of current findings and current findings may not be representative of the whole sub-Saharan region.

Finally, although the present literature review is maybe not fulfilling all methodological criteria to be labeled as systematic, a large number of studies responding to inclusion criteria are included thus we believe present findings are a fair representation of current status of this subject in scientific literature.

A positive desire of procreation persists among HIV-infected women and men and it is modify by a set of biological and psychosocial factors. Measuring and reporting the desires of procreation of HIV-infected individuals is one major input in order to provide this population with an appropriate reproductive health services. Assessing procreation desires

of HIV-infected individuals at diagnosis, at the initiation of antiretroviral treatment and periodically during clinical follow-up could undoubtedly health care service to address more correctly their needs in terms of family planning and therefore prevent risky unintended pregnancies among HIV-infected women.

9.3.2. Incidence of pregnancy

Although lower than in general population, the incidence of pregnancy among HIV-infected women after initiating antiretroviral treatment is high. Moreover, current scientific evidence suggests that the incidence rate of pregnancy increases proportionally to time on antiretroviral treatment. Several biological and psychosocial factors appeared to be associated to the incident pregnancies among HIV-infected women on antiretroviral treatment.

Unsurprisingly biological age appeared to be almost systematically associated with the incidence of pregnancy after antiretroviral treatment initiation. The incidence rate of pregnancy appeared to be higher among younger women (under 25 years old) compared to the incidence rate of pregnancy of their older counterparts. One study suggested that the effect of age remains regardless immunological status at antiretroviral treatment initiation. However, pregnancy appeared to be more frequent among HIV-infected women with improved immunological responses. In addition, the incidence rate of pregnancy was higher among HIV-infected women reporting being in couple, regardless the nature of this engagement.

Notwithstanding, as the incidence rate of pregnancy among HIV-infected women observed a great variation across the different studies consulted, we supposed this large variation is probably owed to the method implemented to the pregnancy detection method. Indeed, as the incident rate of pregnancy of studies detecting pregnancy only by women-self report was lower, it could be induced that maybe an important number of pregnancies may have gone undetected. Pregnancy detection of studies implementing systematic-periodic urine or blood pregnancy test was more accurate and therefore maybe more exhaustive. It is suspected that the estimation of incidence of pregnancy through women-self report is probably an important source of information bias. In addition, several studies estimated the

incidence rate of pregnancy as a secondary outcome, not necessarily related to the principal objective of the study and thus detecting pregnancy was maybe not so rigorous.

Moreover, the differences of the outcomes measured and reality depend in some extent to methodological design of the studies. Estimations of observational cohort studies are probably more close to comprehensive care services reality than randomized control trials. The strict measures of follow-up and data collection implemented are maybe incompatibles with conventional health care services functioning. However, missing data and uncontrolled confounders of retrospective cohort studies reduce quality and reliability of reported outcomes.

The estimation of cumulative incidence rate of pregnancy within prospective cohorts varies according the number of person-years of follow-up, making difficult to compare different outcomes across studies with similar methodological designs. Health care-based clinical observational cohorts have in some extent large periods of follow-up and thus higher denominators in terms of person-year to calculate cumulative incidence. Larger periods of follow-up might induce a higher risk of loss to follow-up and therefore probably an underestimation of the incidence rate of pregnancy. On the other hand, prospective cohort studies conducted within a limited period of time, although accounting maybe for a lower risk of loss to follow-up; these studies account as well for a reduce number of person-year of follow-up and thus probably overestimating the incidence rate of pregnancy.

Although probably less common than in the general population; pregnancy is a frequent event among women of reproductive age after a HIV positive diagnosis. Current scientific evidence suggests that the introduction of ART may have played a role in increasing the incidence rates of pregnancy among HIV-infected women. Moreover, epidemiologic trends point out that the incidence rate of pregnancy increases proportionally to time on ART, suggesting an exposure effect of these drugs on women's fertility. However, whether this positive effect of ART on reproductive functions is due to a direct impact on women's reproductive structures and physiology, indirectly due to the whole restoration of health status affecting women's perception of her life after a positive diagnosis or both is not completely understood and merits further research.

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Incidence of Pregnancy After Antiretroviral Therapy Initiation and Associated Factors in 8 West African Countries

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Introduction: This study aimed at estimating the incidence of pregnancy after antiretroviral therapy (ART) initiation in 8 West African countries over a 10-year period.

Methods: A retrospective analysis was conducted within the international database of the IeDEA West Africa Collaboration. All HIV-infected women aged <50 years and starting ART for their own health between 1998 and 2011 were eligible. Pregnancy after ART initiation was the main outcome and was based on clinical reporting. Poisson regression analysis accounting for country heterogeneity was computed to estimate first pregnancy incidence post-ART and to identify its associated factors. Pregnancy incidence rate ratios were adjusted on country, baseline CD4 count and clinical stage, hemoglobin, age, first ART regimen, and calendar year.

Results: Overall, 29,425 HIV-infected women aged 33 years in median (interquartile range, 28–38) contributed for 84,870 women-years of follow-up to this analysis. The crude incidence of first pregnancy (2304 events) was 2.9 per 100 women-years [95% confidence interval (CI): 2.7 to 3.0], the highest rate being reported among women aged 25–29 years: 4.7 per 100 women-years; 95% CI: 4.3 to 5.1. The overall Kaplan–Meier probability of pregnancy occurrence by the fourth year on ART was 10.9% (95% CI: 10.4 to 11.4) and as high as 28.4% (95% CI: 26.3 to 30.6) among women aged 20–29 years at ART initiation.

Conclusions: The rate of pregnancy occurrence after ART initiation among HIV-infected women living in the West Africa region was high. Family planning services tailored to procreation needs should be provided to all HIV-infected women initiating ART and health consequences carefully monitored in this part of the world.

Key Words: HIV, incident pregnancy, predicting factors, post-ART initiation, Africa

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Members of the IeDEA West Africa Collaboration are listed in Appendix.

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INTRODUCTION

Women of reproductive age constitute the largest population affected by HIV infection in sub-Saharan Africa.[1] The wide availability of antiretroviral therapy (ART) in African settings has considerably decreased morbidity and mortality of many women living with HIV, reducing as well the risk of mother-to-child transmission of HIV.[1,2] We hypothesize that this outstanding improvement of life expectancy of women of childbearing age is positively associated with the increasing procreation desires and fertility rates observed after ART initiation in several settings.[3–5] However, safe motherhood needs are partially met for HIV-infected women, since for instance the access to family planning, antenatal, and postnatal care services of good quality are not fully available in most settings.[6–11] Several studies have showed that fertility desire among childless HIV-affected couples, even if lower than in the general population, is high, especially among younger individuals.[12,13] Indeed, the

pregnancy rate among HIV-infected women increases significantly after ART initiation, and this increase seems proportional to the duration of ART exposure, independently of the use of contraceptive methods.[12–15]

The pregnancy occurrence among HIV-infected women remains a major clinical and public health concern for the following reasons. First, women starting ART for their own health during pregnancy present a higher risk of virological failure than women starting ART while not pregnant.[16] Moreover, HIV infection has been pointed out as a leading indirect cause of maternal death in sub-Saharan Africa,[17–20] increasing the risk of several maternal complications positively associated with maternal death.[21,22] Finally, the vertical risk of HIV transmission has not been eliminated yet, especially in lower income settings. This is primarily due to the failure to reach high levels of linkage and retention throughout the cascade of HIV services for all pregnant, delivering, and breastfeeding women.[23]

In West Africa, although the roll out of ART over the last decade has been slower than elsewhere in the developing world, it has considerably contributed to the overall improvement of survival of HIV-infected women in a context of high fertility. Available information about reproductive health patterns and more specifically demographic trends of fertility among HIV-infected women on ART remains poor in this region however. In this context, the aim of this study was to estimate over a 10-year period the incidence of pregnancy after ART initiation on a large sample of ART-treated HIV-infected women of reproductive age, and to identify the associated factors of pregnancy occurrence after ART initiation in West Africa.

METHODS

The IeDEA West Africa Collaboration

The International epidemiological Database to Evaluate AIDS (IeDEA) initiative (http://www.iedea-hiv.org) is a consortium of leading clinicians and epidemiologists launched in 2006 that has been addressing high-priority research questions and streamline HIV/AIDS research through large pooled regional databases. Its African organization was extensively described elsewhere.[24] This cohort analysis was conducted within the IeDEA West Africa Collaboration (http://mereva.isped.u-bordeaux2.fr/iedea/Accueil.aspx). Fifteen HIV/AIDS adult clinics located within 8 countries participated in this report: Benin (n = 1), Burkina Faso (n = 2), Côte d'Ivoire (n = 5), Gambia (n = 1), Guinea-Bissau (n = 1), Mali (n = 2), Nigeria (n = 2), and Senegal (n = 1). Every 18 months, each cohort submits information to the central coordinating center based in Côte d'Ivoire, using a standardized data format. The data collected capture demographic, clinical, biological, and therapeutic information at baseline and during follow-up visits.

Inclusion/Exclusion Criteria and Study Sample

We conducted a retrospective analysis within the West African cohort database among all HIV-infected women of reproductive age (<50 years) and starting ART for their own health between January 1998 and December 2011 according to in-country ART protocols. Women not reporting any follow-up visit were not retained for this analysis. Additionally, 1 clinic participating to the consortium was not systematically reporting pregnancies within its database and was therefore excluded from this analysis. As we were interested in estimating the incidence of pregnancy after ART initiation, HIV-infected women starting ART for their own health while pregnant were included for this analysis but were left censored 9 months after ART initiation (any prevalent pregnancy that initiated before ART initiation was thus not taken into account). The flow diagram of patients' selection is detailed in Figure 1.

Data Collection and Outcome Definition

All eligible women started ART for their own health fulfilling clinical eligibility criteria established by in-country ART protocols. All of the participating clinics had the capacity to perform CD4 cell counts, hematology, and biochemistry. ART was provided free of charge by the national treatment programs according to their individual treatment algorithms. After entry into care, women were typically followed every 6 months or were seen at in-between visits for any intercurrent illness. CD4 cell counts were measured every 6 months. Baseline CD4 was the measure performed at the time of ART initiation or in the previous 6 months. Women not seen at least 6 months without any transfer or death report were considered lost to follow-up.

Pregnancy diagnosis was considered based on the delay of the last menstruation period according to the woman self-

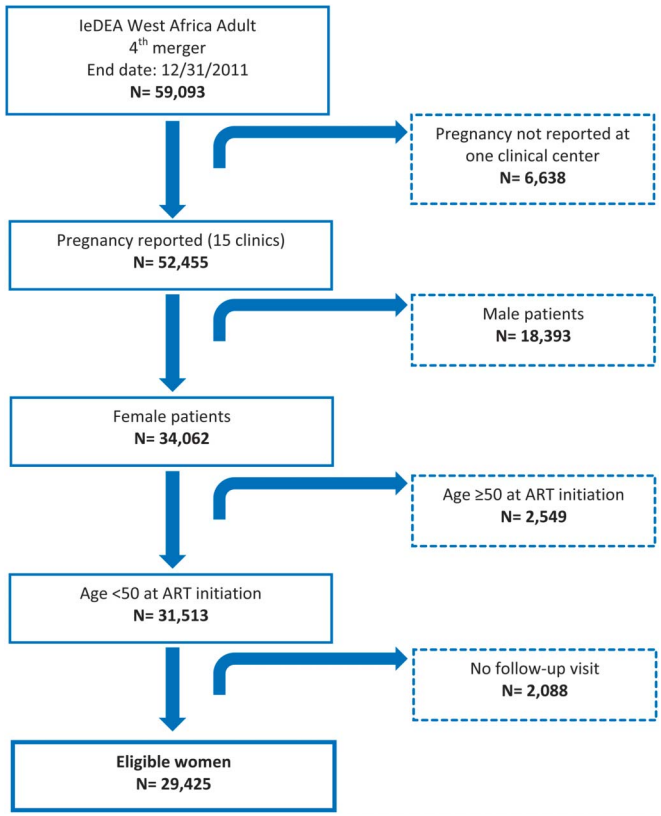


FIGURE 1. Flowchart of women eligible for the pregnancy analysis. The IeDEA West Africa collaboration database, 1998–2011.

report that was assessed at each follow-up visit. The main outcome measure for this analysis was ever becoming pregnant after ART initiation, as reported in the database.

Statistical Analysis

Baseline characteristics were described and compared between pregnant and nonpregnant women using χ^2 test for categorical and qualitative variables and Kruskal–Wallis nonparametric test for continuous variables. Incidence rates of pregnancy event including recurrences were calculated per 100 women-years of follow-up with their 95% confidence interval (CI). Poisson regression method was used to estimate incident rate of first pregnancy among women of reproductive age starting ART as soon as January 15, 1998, until end point date set at December 31, 2011. Each woman included contributed to the denominator from time of ART initiation to their date of pregnancy recording, their last visit or December 31, 2011. Women were right censored at the time of death or loss to follow-up when these events occurred.

Considering pregnancy as a time-dependent event, the probability of becoming pregnant according to the age at ART initiation was estimated using Kaplan–Meier analysis. To identify associated factors of the first pregnancy occurrence after ART initiation, we ran univariable and multivariable Poisson regression models performed with a manual backward selection method, assuming significant all associations with P values <0.05. Maternal age was computed as a time-dependent variable in Poisson regression models. ART history (pretreated or naive) was considered as an explanatory variable. Statistical analyses were generated using SAS software (version 9.2 for Windows, Copyright 2013 for SAS Institute, Inc, Cary, NC).

RESULTS

Overall, 29,425 HIV-infected women accounted for the present analysis, contributing a total of 84,870 women-years of follow-up with 4.4% of death and 25.6% of loss to follow-up across the study period.

Baseline characteristics according to pregnancy experience are detailed in Table 1. Women who reported a pregnancy were significantly younger at ART initiation than those who never reported such an event: 29.7 years in median versus 33.5 years ($P < 0.001$). Similarly, women who were identified as pregnant started ART at higher median CD4 cell count level (191 cells/mm^3) than those who never reported a pregnancy during the study period (172 cells/mm^3) ($P < 0.001$). Pregnancy was less frequent among women who started ART with a clinical stage III/IV or AIDS compared with those starting ART with a less-advanced stage of HIV disease (19.6% vs. 24.5%) ($P < 0.001$). Hemoglobin level at baseline among women becoming pregnant after ART initiation was slightly higher in median than among those who never became pregnant (10.2 vs. 10.1 g/dL; $P = 0.01$).

Pregnancy Occurrence

As detailed in Table 2, 2515 pregnancies were reported among 2304 women during the course of follow-up: 2107 women had 1 pregnancy, 183 had 2 pregnancies, and 14 women reported 3 pregnancies. The crude incidence rate of pregnancy was 2.96 pregnancies per 100 women-years (95% CI: 2.85 to 3.08) (Table 2). The highest rate was reported in Burkina–Faso (3.46 pregnancies per 100 women-years; 95% CI: 3.11 to 3.81), followed by Nigeria (3.43 pregnancies per 100 women-years; 95% CI: 3.19 to 3.66) and Togo (3.35 pregnancies per 100 women-years; 95% CI: 2.57–4.13). For the remaining 5 countries, the incidence rate of pregnancy was below 3.0 pregnancies per 100 women-years.

Median time from ART initiation to the first pregnancy was 24.6 months [interquartile range (IQR), 12.1–43.1]. Among women reporting several pregnancies, the median time between first pregnancy and the second one was 19.7 months (IQR, 13.1–30.3) and 15.3 months (IQR, 14.1–22.1) between the second and the third ones.

As shown also in Table 2, the incidence rate of first pregnancy was 2.85 per 100 women-years (95% CI: 2.74 to 2.97) during the first 12 months after ART initiation and was increasing thereafter. The incidence rate of pregnancy was higher than 4 pregnancies per 100 women-years among women aged between 20 and 34 years, especially among those aged between 25 and 29 years peaking at 4.69 pregnancies per 100 women-years (95% CI: 4.32 to 5.06). For age groups 35–39 years old and 16–19 years old, incidence rate of pregnancy was of 2.74 (95% CI: 2.50 to 2.97) and 1.95 (95% CI: 0.60 to 3.30) pregnancies per 100 women-years, respectively. The lowest incidence rate of pregnancy was estimated in the age group of 40–49 years old [0.53 pregnancies per 100 women-years (95% CI: 0.43 to 0.62)].

As shown in Figure 2, the overall pregnancy probability was 11% by the fourth year on ART; between 19% and 33% among women aged <30 years at ART initiation, around 18% among women aged 30–35 years, and much lower in older women.

As presented in Table 2, incidence rate of first pregnancy after ART initiation among women starting ART with a clinical stage A, B/I, II was 3.20 per 100 women-year (95% CI: 3.04 to 3.35), whereas this figure was lower among women starting ART at more advanced stages of HIV disease. Similarly, the incidence rate of first pregnancy among women starting ART with CD4 cells counts of ≥500 cells per cubic millimeter was 3.72 per 100 women-years (95% CI: 3.05 to 4.38) and decreased proportionally to the severity of immune deficiency at ART initiation. Although not statistically significant, pregnancy tended to be less frequent among women starting ART with lower levels of hemoglobin (Table 2).

Factors Associated With Pregnancy Occurrence

The following factors collected at ART initiation and during follow-up were investigated in multivariable regression analysis to estimate adjusted incidence risk ratios (aIRRs) of the first pregnancy: country, year of starting ART, age (time-dependent variable), clinical stage, baseline CD4 cell count, ART regimen, history of ART, and hemoglobin (Table 3).

When compared with women aged 40–49 years, women aged 16–19, 20–24, 25–29, 30–34, and 35–39 years

TABLE 1. Baseline Characteristics According to Women's Experience of Pregnancy: the IeDEA West Africa Collaboration, 1998–2011

Characteristics at ART Initiation	Women Ever Becoming Pregnant (N = 2304)	Women Never Becoming Pregnant (N = 27,121)	Total (N = 29,425)	*P*
Age in yrs, median (IQR)	29.7 (26.5–32.9)	33.5 (28.9–39.3)	33.1 (28.6–38.8)	<0.0001*
Baseline CD4 count (cells/μL), median (IQR)	191 (108–285)	172 (84–271)	173 (86–272)	<0.0001*
Baseline CD4 count (cells/μL) (%)				<0.0001†
<50	194 (8.4)	3205 (11.8)	3399 (11.6)	
50–99	193 (8.4)	2645 (9.8)	2838 (9.6)	
100–199	527 (22.9)	5763 (21.3)	6290 (21.4)	
200–299	430 (18.7)	4399 (16.2)	4829 (16.4)	
300–349	117 (5.1)	1329 (4.9)	1446 (4.9)	
350–499	143 (6.2)	1453 (5.4)	1596 (5.4)	
≥500	119 (5.2)	1201 (4.4)	1320 (4.5)	
Missing	581 (25.2)	7126 (26.3)	7707 (26.2)	
Hemoglobin (g/dL), median (IQR)	10.2 (9.0–11.4)	10.1 (8.9–11.3)	10.2 (8.9–11.3)	0.0130*
Baseline hemoglobin (g/dL) (%)				0.0028†
≥12	217 (9.4)	2417 (8.9)	2634 (9.0)	
10–12	629 (27.3)	6288 (23.2)	6917 (23.5)	
8–10	455 (19.8)	5155 (19.0)	5610 (19.1)	
<8	147 (6.4)	2070 (7.6)	2217 (7.5)	
Missing	856 (37.2)	11,191 (41.3)	12,047 (40.9)	
WHO or CDC clinical stage (%)				<0.0001†
A, B/I, II	1574 (68.3)	16,617 (61.3)	18,191 (61.8)	
AIDS/III, IV	452 (19.6)	6648 (24.5)	7100 (24.1)	
Missing	278 (12.1)	3856 (14.2)	4134 (14.0)	
Regimen at ART initiation (%)				<0.0001†
2NRTIs + nevirapine	1665 (72.3)	16,584 (61.1)	18,249 (62.0)	
2NRTIs + efavirenz	416 (18.1)	7692 (28.4)	8108 (27.6)	
2NRTIs + PI	156 (6.8)	2115 (7.8)	2271 (7.7)	
3NRTIs	25 (1.1)	359 (1.3)	384 (1.3)	
Other regimens	42 (1.8)	371 (1.4)	413 (1.4)	
History of ART (%)				0.3622†
Naive	2142 (93.0)	25,347 (93.5)	27,489 (93.4)	
Pretreated	162 (7.0)	1774 (6.5)	1936 (6.6)	

*Kruskal–Wallis test.
†χ^2 test.
CDC, US Centers for Disease Control.

had an increased risk of becoming pregnant after ART initiation (aIRR of 3.52, 7.12, 8.26, 7.64, and 5.11, respectively, $P < 0.001$).

Starting ART at an advanced clinical stage of HIV disease (CDC stage C or WHO stages III and IV) reduced significantly the likelihood of pregnancy after ART initiation (aIRR: 0.83; 95% CI: 0.74 to 0.93). CD4 cell count at ART initiation discriminated well the risk of first pregnancy after ART initiation: the higher the CD4 count at ART initiation, the more frequent the subsequent occurrence of pregnancy. Indeed, compared with women starting ART with a CD4 cell count less than 50 cells per cubic millimeter, the aIRR of pregnancy post-ART initiation was 1.14 (95% CI: 0.93 to 1.39), 1.25 (95% CI: 1.06 to 1.48), 1.38 (95% CI: 1.16 to 1.64), 1.35 (95% CI: 1.07 to 1.70), 1.41 (95% CI: 1.13 to 1.76), and 1.43 (95% CI: 1.13 to 1.81) for women starting with CD4 cell count between 50 and 99, 100–199, 200–299, 300–349, 350–499, and ≥500 cells per cubic millimeter, respectively.

Finally, when compared with those initiating ART with a nevirapine-based regimen, HIV-infected women starting ART with an efavirenz-based regimen had a significantly decreased aIRR (0.63, 95% CI: 0.56 to 0.71). The history of Antiretrovirals use did not influence the pregnancy occurrence after ART initiation.

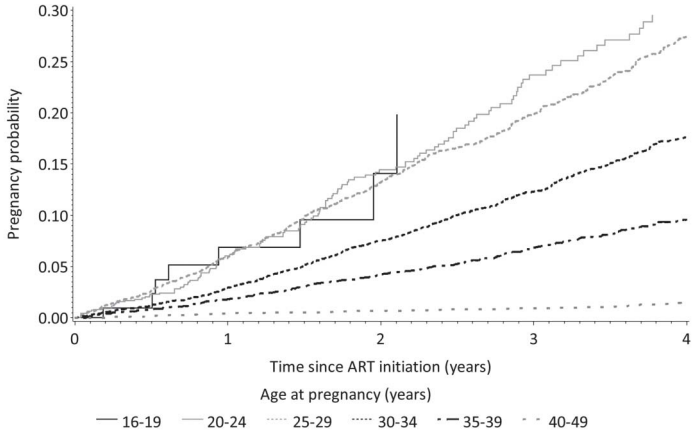
DISCUSSION

This study estimated the occurrence of pregnancy among HIV-infected women after ART initiation at 15 clinical sites in 8 West African countries over a 10-year period. To explain demographic trends of the incidence of pregnancy in this population, we looked as well for epidemiological, clinical, biological, and therapeutic characteristics. According to our findings, the average crude incidence rate of pregnancy after ART initiation was 2.9 pregnancies per 100 women-years. To the best of our

TABLE 2. Pregnancy Incidence According to Country and Women's Baseline Characteristics: the IeDEA West Africa Collaboration, 1998–2011

Country	No. Women (%)	No. First Pregnancies	Incidence of First Pregnancy per 100 Women-Years (95% CI*)	Overall No. Pregnancies	Pregnancy Incidence per 100 Women-Years (95% CI)
Country					
Côte d'Ivoire	10,107 (34.4)	777	2.52 (2.34–2.70)	887	2.71 (2.53–2.89)
Benin	1621 (5.5)	101	2.21 (1.78–2.64)	119	2.41 (1.98–2.84)
Burkina Faso	3685 (12.5)	341	3.33 (2.97–3.68)	379	3.46 (3.11–3.81)
Guinea-Bissau	1130 (3.8)	20	1.20 (0.68–1.73)	22	1.31 (0.76–1.85)
Mali	2447 (8.3)	187	2.45 (2.10–2.81)	202	2.53 (2.18–2.88)
Nigeria	8711 (29.6)	800	3.43 (3.19–3.67)	824	3.43 (3.19–3.66)
Senegal	287 (1.0)	10	2.40 (0.91–3.89)	11	2.51 (1.03–4.00)
Togo	1437 (4.9)	68	3.29 (2.51–4.07)	71	3.35 (2.57–4.13)
Follow-up post-ART (yrs)					
First year on ART	7940 (27.0)	574	2.36 (2.16–2.55)	576	2.36 (2.16–2.55)
Second year on ART	5403 (18.4)	563	2.93 (2.69–3.17)	596	3.17 (2.91–3.42)
Third year on ART	4560 (15.5)	399	2.77 (2.50–3.04)	439	3.18 (2.89–3.48)
Fourth year on ART	3358 (11.4)	318	3.08 (2.74–3.41)	371	3.82 (3.43–4.21)
Fifth year on ART and more	8164 (27.8)	450	2.92 (2.65–3.19)	533	3.67 (3.36–3.99)
Age at pregnancy (yrs)					
40–49	9232 (31.4)	118	0.53 (0.43–0.62)	128	0.57 (0.47–0.66)
35–39	6729 (22.9)	523	2.74 (2.50–2.97)	567	2.79 (2.56–3.02)
30–34	7298 (24.8)	896	4.17 (3.89–4.44)	991	4.29 (4.03–4.56)
25–29	4364 (14.8)	618	4.69 (4.32–5.06)	671	4.78 (4.42–5.15)
20–24	1170 (4.0)	141	4.01 (3.35–4.68)	150	4.11 (3.45–4.76)
16–19	126 (0.4)	8	1.95 (0.60–3.30)	8	1.92 (0.59–3.26)
Missing	506 (1.7)	—		—	
Baseline clinical stage					
A, B/I, II	18,191 (61.8)	1574	3.20 (3.04–3.35)	1712	3.30 (3.14–3.45)
C/III, IV	7100 (24.1)	452	2.33 (2.11–2.54)	500	2.45 (2.23–2.66)
Missing	4134 (14.1)	278	2.30 (2.03–2.57)	303	2.42 (2.15–2.69)
Baseline CD4 count (cells/μL)					
<50	3399 (11.6)	194	2.24 (1.93–2.56)	215	2.39 (2.07–2.71)
50–99	2838 (9.6)	193	2.53 (2.17–2.88)	220	2.74 (2.38–3.10)
100–199	6290 (21.4)	527	3.01 (2.75–3.27)	574	3.10 (2.85–3.36)
200–299	4829 (16.4)	430	3.34 (3.02–3.66)	463	3.41 (3.10–3.72)
300–349	1446 (4.9)	117	3.38 (2.77–4.00)	120	3.31 (2.71–3.90)
350–499	1596 (5.4)	143	3.57 (2.99–4.16)	154	3.63 (3.06–4.21)
≥500	1320 (4.5)	119	3.72 (3.05–4.38)	126	3.73 (3.08–4.38)
Missing	7707 (26.2)	581	2.48 (2.28–2.68)	643	2.62 (2.42–2.82)
First ART regimen					
2NRTIs + NVP	18,249 (62.0)	1665	3.48 (3.31–3.65)	1795	3.56 (3.40–3.73)
2NRTIs + EFV	8108 (27.6)	416	1.75 (1.58–1.91)	468	1.88 (1.71–2.05)
2NRTIs + PI	2271 (7.7)	156	2.41 (2.03–2.79)	179	2.60 (2.22–2.98)
3NRTIs/others	797 (2.7)	67	2.57 (1.96–3.19)	73	2.67 (2.06–3.28)
History of ART					
Naive	27,489 (93.4)	2142	2.86 (2.73–2.98)	2337	2.97 (2.85–3.09)
Pretreated	1936 (6.6)	162	2.82 (2.39–3.25)	178	2.93 (2.50–3.36)
Baseline hemoglobin (g/dL)					
≥12	2634 (9.0)	217	3.11 (2.69–3.52)	232	3.15 (2.75–3.56)
10–12	6917 (23.5)	629	3.28 (3.02–3.54)	698	3.45 (3.19–3.70)
8–10	5610 (19.1)	455	2.94 (2.67–3.21)	494	3.01 (2.75–3.28)
<8	2217 (7.5)	147	2.80 (2.35–3.26)	163	2.96 (2.50–3.41)
Missing	12,047 (40.9)	856	2.53 (2.36–2.70)	928	2.63 (2.46–2.80)
Total cohort		2304	2.85 (2.74–2.97)	2515	2.96 (2.85–3.08)

*95% Confidence Interval.
EFV, efavirenz; NVP, nevirapine; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.



Age at ART initiation (years)	Pregnancy probability (95% confidence interval) by year on ART			
	1st year	2nd year	3rd year	4th year
16-19	0.069 (0.029-0.160)	0.141 (0.062-0.304)	0.198 (0.089-0.405)	0.198 (0.089-0.405)
20-24	0.060 (0.046-0.080)	0.144 (0.118-0.176)	0.237 (0.198-0.282)	0.328 (0.387-0.275)
25-29	0.059 (0.052-0.068)	0.132 (0.120-0.146)	0.199 (0.182-0.216)	0.275 (0.253-0.299)
30-34	0.030 (0.026-0.034)	0.075 (0.068-0.083)	0.123 (0.114-0.133)	0.177 (0.165-0.190)
35-39	0.018 (0.015-0.022)	0.043 (0.037-0.049)	0.069 (0.061-0.078)	0.096 (0.086-0.107)
40-49	0.005 (0.003-0.007)	0.007 (0.005-0.009)	0.009 (0.007-0.012)	0.015 (0.012-0.019)
Total	0.023 (0.021-0.025)	0.052 (0.049-0.055)	0.079 (0.075-0.083)	0.109 (0.104-0.114)

FIGURE 2. Kaplan–Meier probability of pregnancy occurrence after ART initiation according to age at ART initiation. The IeDEA West Africa collaboration, 1998–2011.

knowledge, it is the first time that such a figure is reported in this part of Africa known for its high-fertility patterns and infrequent use of contraceptive methods. Although elevated, the estimated pregnancy incidence we found in this population living with HIV and in care in West Africa was lower than among their uninfected counterparts in the region. Indeed, according to the 2012 African health observatory report, fertility rates across the countries we surveyed ranged between 4 and 6 live births per 1000 women-years.[25] Although this variation might be owed to methodological differences, it may also suggest that fertility patterns are somehow conditioned by HIV infection.

Similarly, it seemed that the incidence rate of pregnancy within our study sample was lower than previous estimations in other sub-Saharan African settings. In Southern Africa, Bussmann et al[26] reported a post-ART pregnancy rate of 7.9 per 100 women-years in Botswana, and Westreich et al[15] reported an incidence rate of pregnancies of 5.2 per 100 women-years after ART initiation in a South African clinical cohort. Furthermore, in rural Uganda, the incidence rate of pregnancy was as high as 9.5 per 100 women-years 24 months after ART initiation.[13] Finally, a larger study conducted by Myer et al reported an overall crude incidence rate of pregnancy after ART initiation of 9.0 per 100 women-years in 7 African countries including Côte d'Ivoire. Although not fully detailed, Myers et al estimation for Côte d'Ivoire appeared higher than the one we found in our study. We suspect that this difference might be owed to the fact that their study was conducted within a network of women-centered clinics focusing on PMTCT of HIV infection, thus, pregnancy was the main outcome measure with probably more accurate and rigorous detection methods.[14]

We also suspect that differences in occurrence of pregnancy after ART initiation between West Africa and other African settings might be due to sociodemographic specificities and HIV disease and care patterns. Methodological variations across studies cannot however be fully excluded. Although systematically confirmed clinically, estimations on incidence rate of pregnancy presented in our study were initially based on women self-report of the last menstruation period. Bearing in mind that miscarriages and abortions are very frequent during the early months of pregnancy[27] and HIV infection has been pointed out as an important cause,[28] we suspect that a substantial number of pregnancies may have gone undetected. The former and the significant proportion of dropouts contributed clearly to an underestimation of the pregnancy incidence reported. Similarly, in this context of large-scale public health program, the data quality did not allow to document how patients break in care in a standardized way across sites. Finally, the lack of information on some potentially important confounding variables (such as marital status, parity, or family planning methods availability or use) limits somewhat the interpretation of our findings.

The incidence rate of pregnancy after ART initiation increased slightly but progressively throughout years in care, suggesting a positive effect of ART on fertility among women of reproductive age, and this association was particularly strong among younger women. This phenomenon is consistent with studies conducted in other sub-Saharan African settings, showing an increased cumulative incidence rate of pregnancy post-ART initiation proportional to time on clinical follow-up.[14,15,26] This finding suggests that the global

TABLE 3. Poisson Regression Univariable and Multivariable Model Estimating Associated Factors of the Incidence Rate of First Pregnancy After ART Initiation (29,425 Women; 84,870 Person-Years): the IeDEA West Africa Collaboration, 1998–2011

		Univariable Models		Multivariable Model	
Predicting Factors	**No. Reported Pregnancies (First Event)**	**Incidence Rate Ratio (95% CI)**	***P***	**Adjusted Incidence Rate Ratio (95% CI)**	***P***
Country			<0.0001		0.0006
Côte d'Ivoire	777	Ref		Ref	
Benin	101	0.88 (0.71–1.08)		0.92 (0.74–1.14)	
Burkina Faso	341	1.32 (1.16–1.50)		1.24 (1.09–1.42)	
Guinea-Bissau	20	0.48 (0.31–0.75)		0.59 (0.38–0.93)	
Mali	187	0.98 (0.83–1.15)		0.90 (0.76–1.08)	
Nigeria	800	1.37 (1.24–1.51)		0.99 (0.89–1.11)	
Senegal	10	0.96 (0.51–1.79)		1.01 (0.54–1.9)	
Togo	68	1.30 (1.01–1.67)		0.83 (0.64–1.08)	
Year of starting ART			<0.0001		<0.0001
<2005	299	Ref		Ref	
2005–2006	722	1.24 (1.09–1.42)		0.89 (0.77–1.04)	
2007–2008	760	1.83 (1.60–2.09)		1.34 (1.15–1.56)	
2009–2011	523	2.16 (1.87–2.49)		1.58 (1.35–1.86)	
Age (yrs, time dependant)			<0.0001		<0.0001
40–49	118	Ref		Ref	
35–39	523	5.26 (4.31–6.42)		5.11 (4.19–6.24)	
30–34	896	8.00 (6.60–9.69)		7.64 (6.30–9.26)	
25–29	618	9.00 (7.39–10.96)		8.26 (6.77–10.07)	
20–24	141	7.71 (6.04–9.85)		7.12 (5.57–9.11)	
16–19	8	3.74 (1.83–7.66)		3.52 (1.72–7.20)	
Clinical stage at ART initiation			<0.0001		<0.0001
A, B/I, II	1574	Ref		Ref	
C/III, IV	452	0.73 (0.66–0.81)		0.83 (0.74–0.93)	
Missing	278	0.72 (0.64–0.82)		0.78 (0.68–0.90)	
CD4 count at ART initiation (cells/μL)			<0.0001		0.0032
<50	194	Ref		Ref	
50–99	193	1.13 (0.92–1.37)		1.14 (0.93–1.39)	
100–199	527	1.34 (1.14–1.58)		1.25 (1.06–1.48)	
200–299	430	1.48 (1.25–1.76)		1.38 (1.16–1.64)	
300–349	117	1.50 (1.19–1.88)		1.35 (1.07–1.70)	
350–499	143	1.58 (1.27–1.96)		1.41 (1.13–1.76)	
≥500	119	1.64 (1.31–2.06)		1.43 (1.13–1.81)	
Missing	581	1.10 (0.94–1.30)		1.38 (1.15–1.66)	
Regimen at ART initiation			<0.0001		<0.0001
2NRTIs + NVP	1665	Ref		Ref	
2NRTIs + EFV	416	0.50 (0.45–0.56)		0.63 (0.56–0.71)	
2NRTIs + PI	156	0.69 (0.59–0.81)		0.86 (0.72–1.02)	
3NRTIs/others	67	0.74 (0.58–0.95)		0.96 (0.75–1.23)	
Hemoglobin at ART initiation (g/dL)			<0.0001		0.0012
≥12	217	Ref		Ref	
10–12	629	0.94 (0.80–1.11)		1.14 (0.97–1.35)	
8–10	455	0.90 (0.73–1.11)		1.11 (0.90–1.38)	
<8	147	1.05 (0.90–1.23)		1.15 (0.98–1.34)	
Missing	856	0.81 (0.70–0.94)		0.90 (0.76–1.06)	
ART history			0.8805		
ART naive	2142	Ref		—	
Pretreated	162	0.99 (0.84–1.16)		—	

EFV, efavirenz; NVP, nevirapine; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

restoration of health status favored by ART and measured by CD4 cell recovery also boosted fertility functions among women of reproductive age. It is also possible that immune restoration owed to ART favored the onset of maternal fetus tolerance mechanism increasing the probability to take a pregnancy to term successfully. However, such a biological association between post-ART health improvement and restoration of fertility functions requires further research to better understand the underlying biological mechanisms and their association with temporal changes in couple and family life experiences.

Additionally, our findings show that both age and clinical/immunological parameters at ART initiation were important predictors of reproductive patterns among HIV-infected women in care. Consistently with other studies, the incidence rate ratio of pregnancy after ART initiation was significantly higher among younger and healthier HIV-infected women than among their older counterparts with a poorer health status.[13–15] However, the increase of the incidence rate of pregnancy after ART initiation reached its peak at 25–29 years old to decrease progressively afterward, suggesting that although ART might have a positive effect on fertility, it remains restricted to biological conditions, respecting human reproductive cycle.

Healthier women at ART initiation were those having the highest probability of becoming pregnant. This association is explained by the fact that their improved health status increases their reproductive ability but also by the fact that an early exposure to ART might limit the HIV-associated risk of miscarriage. This increased incidence risk of pregnancy associated to higher CD4 levels at ART initiation should be better taken into account in strategies such as treatment as prevention promoting universal and early treatment initiation regardless of CD4 levels.

Unintended pregnancy rates are high in sub-Saharan Africa among women of reproductive age and raise major public health concerns among younger women in these settings.[29] We hypothesize that besides the potential benefits of ART on restoring fertility functions, an important number of these pregnancies is owed to the limited capacity of HIV-infected women to manage their procreation desires. Indeed, the unmet needs for family planning among West African women irrespective of their HIV status are as high as 30%.[9,30] It has been pointed out that integrating family planning services into HIV care is an important shortcoming to reduce unintended pregnancy rates among HIV-infected women and eliminate the vertical risk of HIV transmission.[1,31,32]

To conclude, this is one of the first studies estimating incidence rate of pregnancy among a large regional cohort of about 30,000 HIV-infected women initiating ART for their own health and accounting for about 75,000 women-years of follow-up across 8 West African countries. Although lower than in other African settings and probably underestimated, the incidence rate of pregnancy increases proportionally after ART initiation in West Africa. Moreover, pregnancy after ART initiation remains an event, particularly for younger women, with potentially important individual and public health consequences. As universal access to ART has enabled HIV-infected women of reproductive age to live longer and with higher quality of life standards, childbearing is a growing desire among this population. Understanding the dynamics of fertility among women on ART is a key step to correctly fit the strategies of integrating family planning into HIV care and to help HIV-infected women to correctly fulfill their procreation trajectory through safe and adapted motherhoods programs. This is one of the many challenges that HIV care and treatment programs must address upfront now, especially in West Africa.

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APPENDIX. The IeDEA WEST AFRICA COLLABORATION STUDY GROUP (AS OF NOVEMBER 2013)

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10. Repercussions of pregnancy on health status of HIV-infected women of reproductive age

10.1. Introduction

As discussed in the previous chapter, an HIV diagnosis does not necessarily cease the desires of childbearing, and many HIV-infected women and men chose to procreate, particularly after starting ART. This persistent positive desire of childbearing expressed by HIV-infected individuals is somewhat reflected in the incidence rates of pregnancy observed in observational studies conducted within clinical cohorts of HIV infected individuals. Although incidence rate of pregnancy among HIV-infected women is probably lower than in general population, pregnancy is not an uncommon event among this population. Moreover, this incidence rate of pregnancy seems to increase proportionally to time on follow-up for women on antiretroviral treatment.

Given that pregnancy is a major biological and psychosocial event in women life with potential repercussions on women health. Besides the risk of transmission of HIV infection during pregnancy from mothers to their babies, I hypothesized that pregnancy could be a major health challenge for HIV infected women and their babies. The increased metabolic demand occurring during pregnancy may probably have important repercussions on HIV-infected women immune system, weakened already by HIV infection and, therefore probably accelerating HIV-disease progression. This potential negative effect on women's immune response could probably provoke a higher susceptibility to opportunistic diseases threatening women and children lives.

Current scientific literature points out as well that HIV infection is associated with a higher risk of maternal mortality. In settings with high HIV prevalence, an important fraction of maternal deaths are owed to the HIV infection. However, the mechanism explaining the association between HIV infection and the risk of maternal death is not fully understood. Current research is inconclusive in terms of whether pregnancy increases the risk of HIV-disease progression or HIV-infection increase the risk of fatal maternal complications.

The objective of the following section is to firstly present an epidemiologic update of maternal mortality, which is a major cause of death among women of reproductive age.

Within this epidemiologic update, I present current epidemiologic trends, geographic distribution and major maternal causes of death. Secondly, based on current scientific literature, I present a review of current scientific literature aiming at investigating whether or not HIV infection is associated with a higher risk of death during pregnancy or postpartum and the possible mechanisms explaining this association. Finally, I close this section with the third peer-reviewed article of this doctoral research framework aiming at estimating the risk of death, HIV-disease progression and/or loss to follow-up according to pregnancy occurrence among women on ART, conducted within the IeDEA West Africa observational cohort.

10.2. Epidemiologic background of maternal mortality

Maternal mortality is defined as the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes(236).

Estimations from early nineties indicated that around 585,000 women died of maternal-related causes worldwide(237). Moreover, desegregated data showed that a great disparity existed across regions and almost the totality (582,000) of overall maternal deaths were reported by low-and-middle resources settings(237). Alarmingly, around 40 per cent of all these deaths occurred in the African continent, setting where one women out of sixteen died of maternal causes(237, 238).

These deaths were mostly due to pregnancy, delivery and postpartum complications which were not correctly managed(237, 238). The most of these maternal deaths can be averted if births are attended by skilled health personnel, have the proper equipment and supplies, and can refer women in a timely manner to emergency obstetric care when complications are diagnosed(237, 238). Complications require prompt access to quality obstetric services equipped with life-saving drugs, including antibiotics, and the ability to provide blood transfusions needed to perform Caesarean sections or other surgical interventions(237, 238). Additional scientific evidence suggests as well that the reducing the gap in terms of unmet needs of family planning could avert a significantly high number of maternal deaths in low-and-middle resource settings(94).

It is worth to note as well that maternal mortality rate was higher African settings than anywhere else worldwide and, particularly and strikingly higher in settings at the South of the Sahara. It was estimated that in certain sub-Saharan Africa regions one out of twelve women died of maternal causes (237, 238). At the end of past century, these alarming estimations raised great awareness within the global community and, taking action in order to reduce these estimations became one major public health priority. The reduction of maternal mortality by half from 1990 levels by the year 2000 was adopted as common goal of WHO and UNICEF(238).

As by the deadline year this goal remained unachieved, the global community set out this goal once again within the Millennium Declaration as a part of the eight Millennium Development Goals. Reduce by three quarters maternal mortality ratio worldwide by 2015, was the ambitious target set out within The Millennium Declaration.

Since the reduction of maternal mortality ratio by three quarters by 2015 was embraced by the global community as one Millennium Development Goals target and the global action plan was rolled out; trends of maternal mortality have sensibly changed. Recent estimations point out that, although the goal will not be completely achieved worldwide by 2015 as expected, great progress has been achieved.

10.3. Current global status

Globally, the maternal mortality ratio decreased by 55 per cent over the last two decades, from 523 000 in 1990 to 289 000 in 2013(10, 53, 236, 238).Within this period the global rate of decline in the maternal mortality ratio is of 3.1 per cent per year, just over a half of what needed to achieve the Millennium Development Goal by 2015 (53, 236). As shown in figure 23, although this decline was significant for all WHO regions in 2010, it happened at different rates.

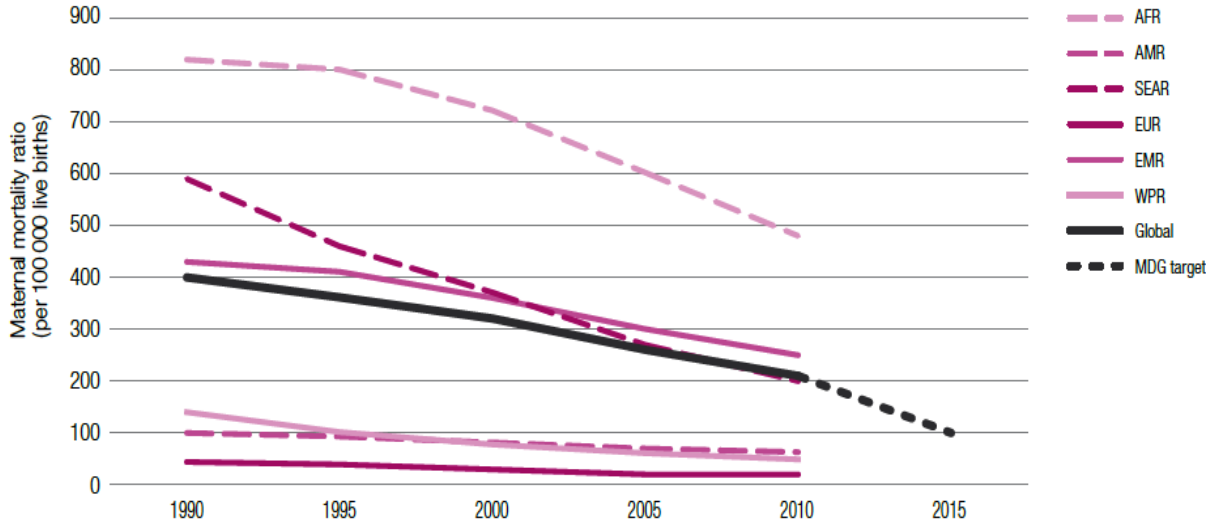

Figure 23. Regional and global trends in maternal mortality ratio 1990 – 2010. (Source: WHO, 2013)

Important disparities remain between developed and low-and middle income settings. Over 800 women died every day from avoidable maternal causes and almost 99% (286 000) of these deaths occurred in developing countries(53, 238).

As shown in figure 24, in 2013 sub-Saharan Africa was the region reporting the highest maternal mortality ratio worldwide. Maternal mortality ratio (MMR) varies across the different sub-Saharan African sub-regions. Western Africa (540 000) and Central Africa (680 000) are the two regions reporting the highest Maternal Mortality Ratios (MMR) whereas, Eastern Africa (440 000) and Southern Africa (160 000) maternal mortality ratios are somewhat lower(236).

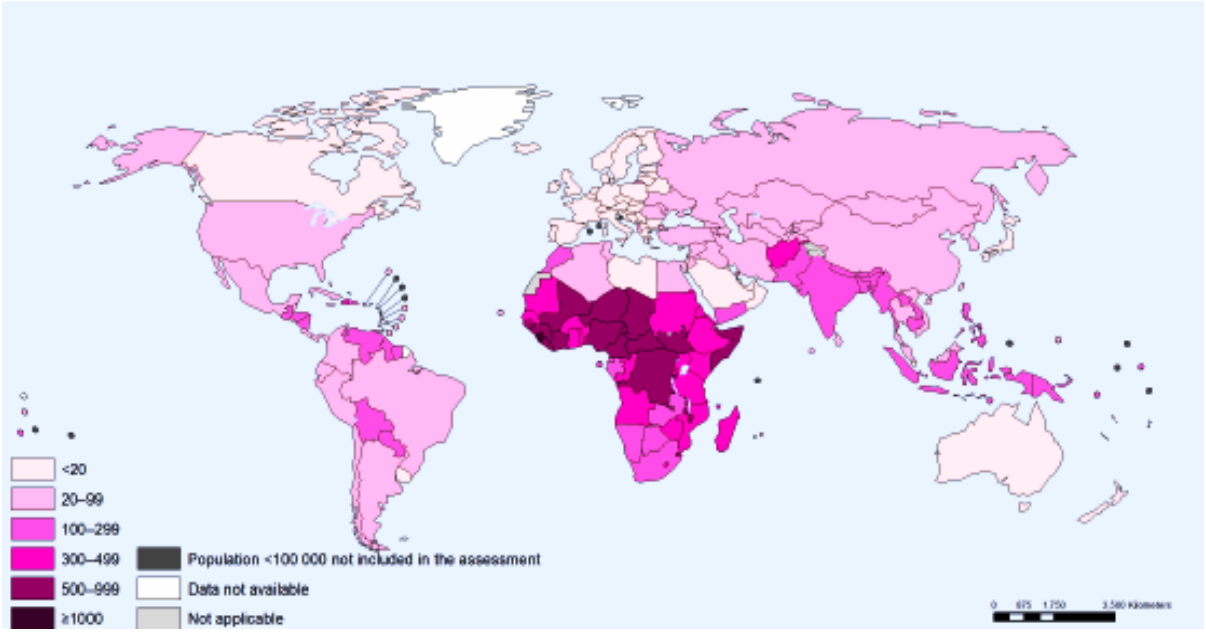

Figure 24. Maternal mortality ratio (maternal deaths per 100,000 live births in women aged 15 to 49), 2013. (Source: UNICEF, 2013)

Global and regional estimations tends to mask disparities within and among countries, more desegregated estimations point out that over half of all maternal deaths are reported by seven countries(238). Four out of these seven countries are located in sub-Saharan Africa, the other three in South-East Asia.

Out of these seven countries, two countries accounted for 30 per cent of all maternal deaths worldwide: India with a maternal mortality ration of 50,000 maternal deaths and Nigeria with 40 000 accounted for 17 and 14 per cent respectively (236, 238). Democratic Republic of the Congo (21 000, 7%); Ethiopia (13 000, 4%); Indonesia (8800, 3%); Pakistan (7900, 3%); United Republic of Tanzania (7900, 3%) are the remaining countries reporting the highest number of maternal deaths (figure 25)(236, 238).

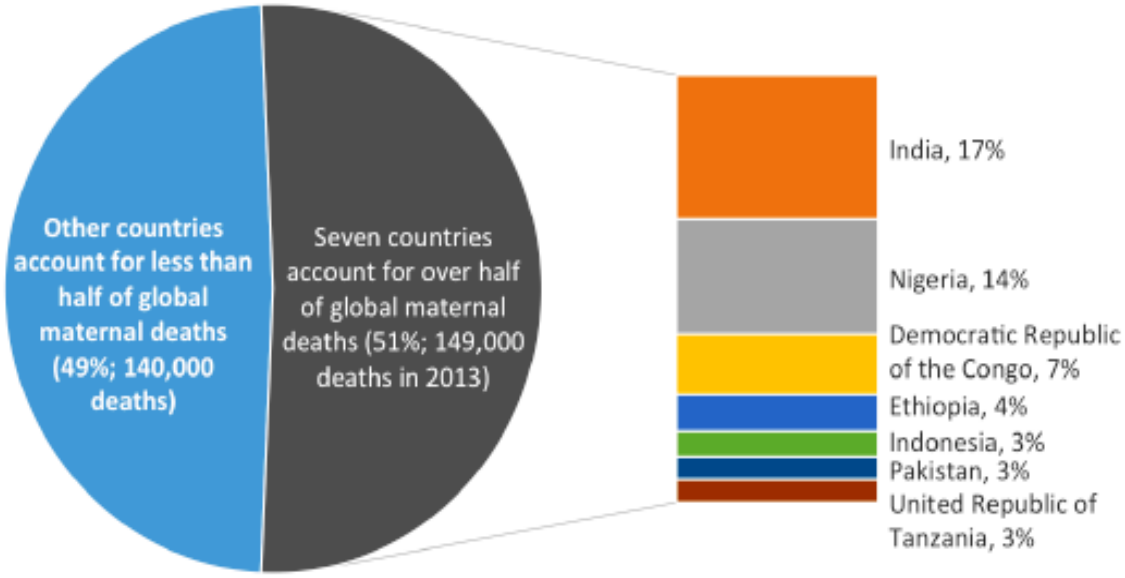

Figure 25. Proportion of global maternal deaths in the seven countries with highest numbers of maternal deaths. (Source: UNICEF, 2013)

Additionally, the ranking of the highest maternal mortality ratios is leaded by ten sub-Saharan African countries: Sierra Leone (1,100 per 100,000 live births), Chad (980,000), Central African Republic (880,000), Somalia (850,000), Burundi (740,000), Democratic Republic of the Congo (730,000), South Sudan (730,000), Côte d'Ivoire (720,000), Guinea (650,000) and Liberia (640,000) (236). Only two countries outside the sub-Saharan African region had high MMR: Afghanistan (400,000) and Haiti (380,000) (236).

Finally, according to current estimations lifetime risk of maternal death, which is a population indicator expressing the probability that a 15-year-old women will die eventually from a maternal cause, has observed an important reduction at a global level(237). Within ten years the lifetime risk of maternal death decreased of more than the half. In 1990, one woman out of 60 was at risk of dying of maternal causes whereas in 2013, it was of 1 woman out of 190 (237). However, this indicator observes important disparities across different world regions.

In industrialized countries, the lifetime risk of maternal death is one in 3,700 whereas in least developed countries this risk is of one in 160 (237). Alarmingly, the estimated lifetime risk of dying of maternal causes for sub-Saharan African women is as high as one woman in 38(237). Within the sub-Saharan region, Chad and Somalia had the highest life time risks of maternal mortality reporting at 1 in 15 and 1 in 18, respectively (237).

10.4. Progress towards achievement of the 5th MDG: Improve maternal health

In order to track the progress of the achievement of 5th MDG, assessments of the mortality rate ratio are conducted periodically at all levels. To achieve a reduction of 75% of maternal mortality rates by 2015, it is expected that countries reduce their annual mortality rate ratio by 5.5%.

According to recent estimations, the global annual rate of decline increased from 2.2% over the years 1990-2005 to 3.3% from 2005 to 2013. Regarding least developed countries, maternal mortality ratio declined from 2.9% between 1990 and 2005 to 3.9% between 2005 and 2013. However, significant differences have been observed among regions (figure 26).

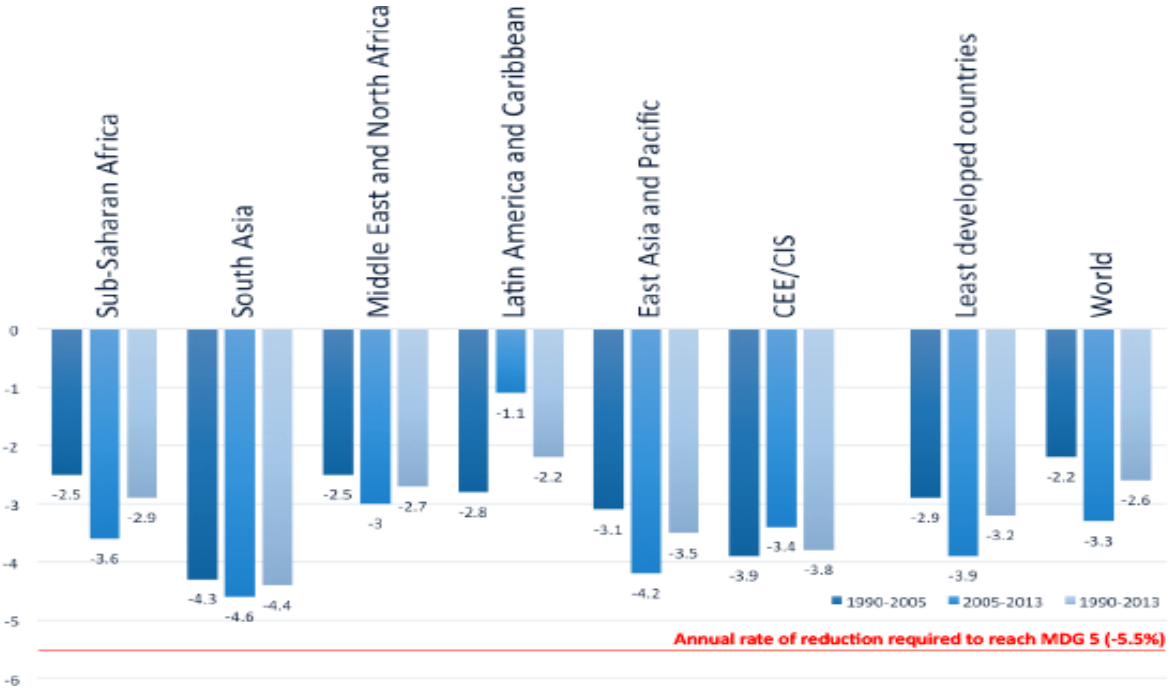

Figure 26. Percentage annual rate of reduction in the maternal mortality ratio, by region. (Source: UNICEF, 2014)

South Asia leads with the highest annual declines of maternal mortality ratio. In this region the annual mortality rate ratio declined increased from 4.3 per cent between 1990 and 2005 to 4.6 between 2005 and 2013. Latin America and the Caribbean, the annual decline decreased of 1.7 between 2005 and 2013. Sub-Saharan Africa, although far still from global target, maternal mortality ratio decline, increased of 1.1 per cent between 2005 and 2013 (236, 238).

At a country level, 19 countries have achieved The Millennium Development target by 2013:

- **African countries:** Equatorial Guinea (81%); Eritrea (77%); Cabo Verde (77%); Rwanda (76%).
- **Asian countries:** Maldives (93%); Bhutan (87%); Cambodia (86%); Lao People's Democratic Republic (80%); Timor-Leste (78%); Nepal (76%).
- **Eastern and central Europe:** Belarus (96% reduction in MMR); Poland (81%); Romania (80%); Bulgaria (78%); Estonia (78%); Latvia (77%);
- **Middle East:** Israel (84%); Oman (77%); Lebanon (76%);

Eleven countries among these are indicated as "On Track" to achieve MDG 5, 63 countries were categorized as "Making Progress" and 13 countries have made "insufficient progress". To conclude, although during last ten years an impressive progress has been achieved in terms of reduction of maternal mortality worldwide, a great effort is still needed to fully achieve the global target of reducing maternal mortality of 75% by 2015. Low-and-middle income settings scores for the highest maternal mortality ratios when compared to industrialized settings. South-East Asia leads the score in terms of reduction of maternal mortality and is the world region more plausible of achieving this goal by the deadline set. Despite sub-Saharan Africa has reported important progress in achieving this goal, this region holds the highest maternal mortality rate and is the least plausible of achieving the 5th Millennium Goal of reducing maternal mortality by three-quarters by 2015.

10.5. Causes of maternal mortality

According to the etiology and physiopathology, the World Health Organization (WHO) classifies the causes of maternal death into two categories: Direct and indirect causes(236). Direct maternal deaths are those resulting from obstetric complications of pregnant state, specific interventions, omissions, incorrect management or a succession of events resulting from any of the former situations(236). Hypertensive disorders, obstetric hemorrhage or complications of C-section surgery are examples of direct causes of maternal death (236).

Indirect maternal deaths are those resulting from previously existing diseases, or from diseases that developed during pregnancy and that were not due to direct obstetric causes but aggravated by physiological effects of pregnancy(236). Deaths due to the aggravation of an existing cardiac or renal disease or chronic infections such as HIV are typical examples of indirect causes of maternal deaths(236).

The concept of “death during pregnancy, childbirth and the puerperium” also called “pregnancy-related death” is an alternative concept related to maternal death, defined as any death temporal to pregnancy, childbirth or the postpartum period, even if it is due to accidental or incidental causes(236). This alternative classification allows the measurement of deaths that are related to pregnancy, even though they do not fulfill strictly the standard definition of maternal death. This alternative definition is particularly useful in settings where the causes of death cannot be accurately verified or are not available in medical certificates(236).

The concept of pregnancy-related deaths are commonly used in population-based surveys, where respondent cannot provide precise information of the causes of deaths but they can provide information about the pregnancy status of the reproductive-aged sibling at the time of death (236). Rather than the measure of maternal death, these surveys provide the measure of pregnancy-related deaths. Although not fully reliable, this measure provides an approximation of maternal death, adapted to the methodological limits of these surveys (236).

Furthermore, as complications of pregnancy and/or childbirth can lead to death beyond the six weeks postpartum period and; current technology and modern procedures enable women to survive adverse outcomes of pregnancy and delivery delaying death beyond 42

days postpartum (236). In certain routine civil registration forms, these deaths do not count as maternal death although they are owed to pregnancy-related event. In order to capture delayed maternal deaths occurring between six weeks and one year postpartum, several maternal deaths assessments use this definition.

10.6. Epidemiology of maternal causes of death

According to recent estimations, 73% of all maternal deaths between 2003 and 2009 were owed to direct obstetric causes whereas indirect causes were responsible of the remaining quart of all maternal deaths from known causes. Among the direct causes, hemorrhage has been the leading cause of maternal death worldwide over the last decade, representing almost one third of all maternal deaths (27.1%) in 2014(238-240). Postpartum hemorrhage was responsible of more than 60% of all reported cases of Hemorrhage (240).

The second leading direct cause of maternal death worldwide was hypertension accounting for 14% of overall rate (239, 240). Sepsis, abortion and embolism together with other direct causes were responsible of 11%, 8% and 13% respectively of overall maternal deaths worldwide (figure 27)(240). Furthermore, obstructed labor and complications of delivery were responsible of 23% of all maternal deaths worldwide each (240). In figure 25, these two causes are included in "Other direct causes" category, which represented 10% of the total (238, 240).

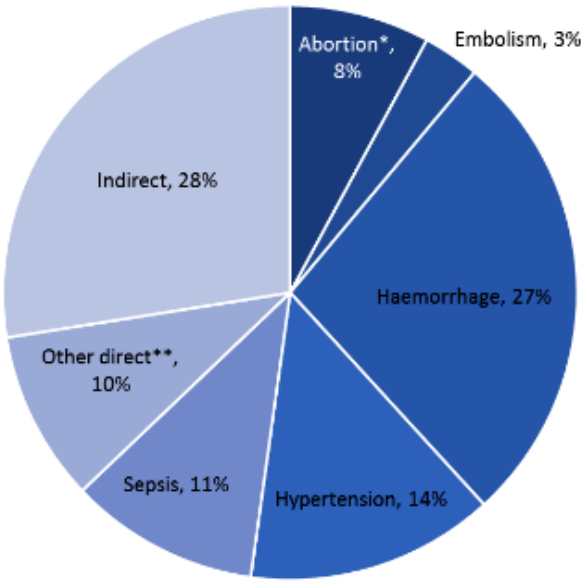

Figure 27. Global distribution of the causes of maternal death. (Source: UNICEF, 2014)
*Nearly 99% of abortion deaths are due to unsafe abortions.
**This category includes deaths due to obstructed labor or anemia.

Geographic distribution of maternal deaths causes is importantly affected by the high epidemiologic burden of this phenomenon observed in sub-Saharan Africa and southern Asia, regions accounting for 84% of all maternal deaths(240). Desegregated data showed that embolism is an important cause of maternal death in developed regions compared to developing regions, where this condition is not commonly diagnosed and reported (240). Moreover, although hemorrhage is the leading cause of maternal death worldwide; the contribution of this condition to overall maternal deaths in northern Africa is of 36%, higher than anywhere else (240). Hypertensive disorders appeared to be a particularly important cause of maternal deaths in Latin America and the Caribbean, with a contribution of 22% to overall maternal deaths in this region (240).

Concerning the indirect causes of maternal deaths, more than three thirds of these deaths were due to pre-existing disorders. These pre-existing disorders included HIV infection, which alone contributed with 5.5% to all maternal deaths dues to indirect causes worldwide (238, 240). Unsurprisingly, the contribution of HIV to the number of maternal deaths owed to indirect causes in settings with high prevalence rates of the infection was sensibly higher. The contribution of HIV infection to overall maternal deaths in sub-Saharan Africa is of 6.4%, higher than any other region worldwide (240). The contribution of HIV to maternal deaths in the remaining regions reached barely 5% (240).

In sub-Saharan Africa, HIV infection is considered one major indirect cause of maternal mortality in this setting (5, 24, 241). Recent estimations pointed out that the risk of death among HIV-infected pregnant and postpartum women is eight times higher than their uninfected counterparts (24). These estimations predicted that roughly 24% of overall maternal deaths in sub-Saharan Africa are attributable to HIV-infection (24).

10.7. HIV infection and maternal mortality

The underlying mechanism explaining the morbid association between HIV-infection and maternal mortality is not completely elucidated and is still subject of debate. On the one hand, it has been suggested that pregnancy itself, might accelerate HIV disease progression of HIV-infected women through interactions between the physiopathology of the viral infection and the pregnancy-related metabolic changes. On the other hand, it has been suspected that HIV-infection could be associated with an increased risk of developing lethal obstetric complications. The following sections will aim at presenting scientific evidence underpinning both mechanisms and then discussing the limitations of these findings.

10.7.1. Association of pregnancy on HIV disease progression or death

Pregnancy is considered a major health event in women's lives, with potential harmful repercussions for HIV-infected women health. It has been widely recognized the major role played by HIV infection increasing the risk of maternal death in sub-Saharan Africa and several research studies aiming at explaining the causal mechanisms of this association has been conducted.

These studies identified HIV disease progression as the diagnosis of any AIDS-defining condition following a positive pregnancy status. According to findings of Westreich et al, within an observational cohort of south African women on antiretroviral treatment, pregnancy was not associated with an increased risk of death or any AIDS-related morbid event (242). Indeed, findings of Westreich et al showed that the risk of death or progressing to a disease stage 4 for HIV-infected women who became pregnant following the initiation of antiretroviral treatment was of aHR: 0.87 (95%CI: 0.51-1.49). Consistently, a similar study conducted by Tai et al reported that the risk of AIDS disease progression decreased significantly of 60% among HIV-infected women who became pregnant after initiating antiretroviral treatment (aHR: 0.40; 95%CI:[0.21-0.76](243). Similar findings were reported by Kaplan et al. and Myer et al. in others South African cohorts of HIV-infected women(244, 245). These findings are underpinned by a literature review on the subject which concluded not finding a significant association between pregnancy and an increased risk of HIV-disease progression among women on ART(246).

However, it is worth to note that, within these cohort studies, , we believe there are major shortcomings to the reliability of these findings since pregnancy detection was based on

women self-report and thus probably not exhaustive, plus a high proportion of women were reported loss to follow-up . Moreover, as the risk period of these studies was unrestricted, we believe their estimations correspond more to a pregnancy-related risk of death rather than a risk of maternal mortality.

On the light of such findings, it has been hypothesized that among HIV-infected women on ART, pregnancy might probably modify the immunological response to ART treatment. To explain this phenomenon and according to literature, three possible reasons were proposed: 1) a potential immunologic boost associated with pregnancy; 2) A selection bias whereby women who are healthier (and thus less likely to have HIV disease progression) are more likely to become pregnant; 3) Adherence to HAART regimens during pregnancy may improve due to increased concern about the well-being of the fetus and/or due to increased contact with the healthcare system for prenatal care(246, 247).

However, recent findings of Matthews et al. within a Ugandan cohort of HIV-infected women on ART tend to contradict the above-mentioned findings. Indeed, within this Ugandan cohort, pregnancy and postpartum periods appeared to be associated with an increased risk of mortality, (248). In addition, the risk of death associated with pregnancy and postpartum was outstandingly high during first year after ART initiation (aHR: 21.48, 95% CI: 3.73-123.51), and decreased proportionally to time on ART (248).

Moreover, within this Ugandan cohort the causes of death were mostly AIDS-related conditions (Tuberculosis, Cryptococcus meningitis and Kaposi sarcoma)(248). These findings suggest probably an important immunosuppression during pregnancy(249, 250) or an increased risk of immune reconstitution inflammatory syndrome (IRIS) owed to the reverse effect during postpartum of the relative immunosuppression provoked by pregnancy(251). Although these findings seems to be sounding, pregnancy detection was based on women self-report thus an unknown number of pregnancy may have gone undetected. In addition, according to authors, the post-partum period was not captured at the enrollment producing probably an information bias and therefore underestimating the time at risk.

The repercussions of pregnancy on immune response have been also subject of several studies. Findings of studies on this concern conducted among ART-naïve women suggested that pregnancy might accelerate the progression of HIV disease through a more rapid depletion of immune system (252-254). However, the restricted number of participants (16

women)(252) and the particular heterogeneity of the study population (more than 50% of injecting drug users)(254), implies a careful interpretation of these findings.

Findings from more recent studies, aiming at estimating the repercussions of pregnancy on immune status of HIV-infected women are somewhat different. According to these studies, CD4 cells declines during pregnancy are temporary and not sustained in postpartum period among ART-naïve women (255-257). Moreover, it appeared that immunological depletion after delivery was uncommon among ART naïve women who had relatively high CD4 cell counts during pregnancy (>500 cell/mm3)(258). Finally, it was underscored that ART naïve women with high initial CD4 count (>500 cells/mm3) had a protracted time (5-7 years) before they reach therapeutic thresholds after pregnancy (259).

However, a study conducted by Westreich et al aiming at exploring the repercussion of pregnancy on a sustained viral suppression. According to the findings of this study pregnancy after initiating antiretroviral treatment was associated with a modest increase of viral failure(193). The risk of virologic failure among HIV-infected women becoming pregnant following initiation of antiretroviral treatment increased significantly of 35% compared to those who never became pregnant. This study suggests as well that an incident pregnancy following the initiation of antiretroviral treatment could increase significantly the risk of virologic failure of 6% by five years.

10.7.2. Association of HIV with lethal direct obstetric complications

HIV infection has been also associated to an increased risk of developing high deadly direct obstetric complications. In sub-Saharan Africa, were HIV-infection is highly prevalent this could be a major threat for women of reproductive age. There is a growing body of scientific evidence aiming at measuring the association of HIV infection and the risk of developing lethal obstetric complications and; understanding the underlying mechanisms probably explaining this phenomenon.

According to a meta-analysis conducted by Calvert et al., HIV increases the risk of intrauterine infections during pregnancy, delivery or the postpartum. HIV-infected women had over three times the risk of a puerperal sepsis compared with uninfected women whether they delivered by C-section or vaginal(260). Additional findings of these meta-analysis pointed out that this risk increased by roughly six times among studies only

including women who delivered by C-section(260). This finding is not surprising since HIV-related immunosuppression may lead to an increased risk of infection among infected women(261). According to the 2005–2007 Saving Mothers report in South Africa, 71% of deaths due to pregnancy-related sepsis occurred in HIV-infected women(262). However, whether the excess risk of endometritis and puerperal sepsis in the intra- and postpartum period is directly attributable to the pregnancy or indirectly related to HIV or AIDS-associated infections remains uncertain(260).

HIV-infection has been also suggested to be associated with an increased risk of developing pre-eclampsia – severe metabolic syndrome of unknown etiology occurring during pregnancy, delivery or postpartum characterized by hypertension and proteinuria –, this association was particularly strong among women on ART. However, current scientific evidence is somewhat contradictory.

On the one hand, within the systematic review and meta-analysis conducted by Calvert C et al, HIV infection was found positively associated with pregnancy-induced hypertension but not with pre-eclampsia and eclampsia(260). On the other hand, a study conducted by Suy et al within an European cohort of HIV-infected women, findings pointed out that HIV-infected women on ART who became pregnant have an increased risk of developing pre-eclampsia compared to their untreated counterparts (263). Similarly and consistently with this finding, Powis et al, found within Mma Bana study that, pregnant women with high levels of viral loads (>100 000 copies/mm3) have higher risk of developing pre-eclampsia(264).

Although the mechanism explaining the onset of pre-eclamptic syndrome is not fully understood, it is suspected to be triggered by an autoimmune reaction(264). Thus, ART-related immunologic restoration might be probably associated with a higher risk of developing pre-eclamptic syndrome (263).

Finally, whilst HIV was associated with an increased risk of antepartum hemorrhage, there was no evidence of an increased risk of placenta praevia, placental abruption, postpartum hemorrhage or retained placenta(191). In addition, an association between HIV and both uterine rupture and prolonged labor was observed, but not between HIV and other complications of dystocia(191).

10.8. Discussion on maternal mortality in the context of HIV infection

Maternal mortality remains one important cause of death among women of reproductive age worldwide. Since the goal of reducing maternal mortality ratio by three-quarters by 2015 was embraced by the global community, great progress has been achieved worldwide towards achieving this goal. Although all regions have reported important achievements towards this goal, the progress is unequal. The highest maternal mortality rates have been estimated in low-and-middle income settings. Sub-Saharan Africa is the setting reporting the highest maternal mortality rate worldwide. No other region in the world as far as sub-Saharan Africa of achieving the fifth Millennium Development Goal by 2015.

The vast majority of maternal deaths are owed to direct causes which are responsible of roughly three-quarts of overall maternal mortality worldwide. Among the direct causes of maternal death, 27% are owed to hemorrhage which is leading direct cause of maternal death worldwide. Following hemorrhage, hypertensive disorders and sepsis are the second most frequently reported causes of maternal death. Among the indirect causes of maternal death, HIV infection is one leading cause responsible of roughly 5% of all maternal deaths worldwide. In high HIV prevalence levels, almost one quart of all maternal deaths is attributable to this infection. Indeed, according to current estimations, HIV-infected pregnant women have a risk of death eight times higher than their uninfected counterparts.

However, findings of current research aiming at estimating the pregnancy-related risk of death among HIV-infected women are somewhat contradicting. Findings of several research studies conducted in observational cohorts of HIV-infected women suggest that pregnancy is not associated with an increased risk of death whereas some others suggest an increased risk of death associated with pregnancy. Within the study we conducted in the IeDEA West Africa observational cohort, pregnancy was not associated with an increased risk of death among HIV-infected women.

However, owed to different methodological limitations these studies are not conclusive. Firstly, as the detection of the outcome pregnancy is based on women self-report, it is not impossible that an important number of events could have gone undetected. Secondly, it is not uncommon that in observational clinical cohorts the event pregnancy is not fully documented. Finally, gestational age at time of pregnancy detection and the date of end of

pregnancy are not systematically documented limiting the correct estimation of the risk period.

To summarize, maternal mortality is an important cause of death among women of reproductive age. HIV infection has been suggested one leading indirect cause of maternal death. HIV-infected women face a higher risk of dying of maternal causes than their uninfected peers and an important fraction of maternal death rates in settings with high HIV prevalence is owed to the infection. Although current scientific evidence is not conclusive in demonstrating the association of pregnancy with a higher risk of death among HIV-infected women on treatment, a potential association is suspected. Similarly, current research suggests as well that pregnancy may have repercussions in terms of immune response of HIV-infected women on antiretroviral treatment.

Although more research is needed to clearly understand the association of HIV infection with the risk of maternal mortality and its underlying mechanisms, current findings are of major public health concern. As pregnancy is not an uncommon event among HIV-infected women on antiretroviral treatment, more clinical scientific knowledge is needed to correctly manage pregnancy under these circumstances, preventing potential risk for children and mothers. This knowledge is a key input to the successful achievement of the targets set out in the global plan of elimination of new HIV pediatric infections and keeping the mothers alive.

Box 4. Estimation of Maternal Mortality. Concepts review.

In order to better understand the concepts utilized to measure and compare levels of maternal mortality around the world it is important to understand the different concepts used to define this topic. According to WHO Health Metrics and Evaluation System, Following measures are the standard measures used to present maternal mortality:

- **Maternal death:** Is the death of a woman while pregnant or within the 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes.

- **Pregnancy-related deaths:** The death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the cause of death.

- **Late maternal death:** the death of a woman from direct or indirect cause, more than 42 days but less than one year after termination of pregnancy.

Measures of maternal mortality

The measure of maternal mortality in a population is essentially estimated using two principal factors: 1) The risk of death in a single pregnancy or a single live birth; 2) The fertility level (the number of pregnancies or births that are experienced by women of reproductive age. These two parameters allow the estimation of three main indicators that yield approximately the number of maternal deaths:

- **Maternal Mortality Ratio (MMR):** defined as the number of maternal deaths during a given time period per 100,000 live births during the same period. This concept captures essentially the risk of death in a single pregnancy or single live birth.

- **Maternal Mortality Rate (MMRate):** defined as the number of maternal deaths in a given period per 1000 women of reproductive age during the same time period.

- **Adult lifetime risk of maternal death**: is the probability that a 15-year-old women will die eventually from a maternal cause.

- **Proportion of deaths among women of reproductive age that are due to maternal causes:** is the number of maternal deaths in a given time period divided by the total deaths among women aged 15-49 years.

Pregnancy after ART initiation in West Africa: Association with retention in care, AIDS, death and immune recovery

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Abstract

Objective: The objective of this study was to determine whether pregnancy has an impact on the long-term clinical outcomes among women becoming pregnant post-ART initiation in West Africa.

Design: This cohort analysis was conducted within the IeDEA West Africa collaboration. All HIV-infected women aged <50 years old, starting ART for their own health in 9 West-African countries. The effect of pregnancy (time dependent variable) on loss to follow-up (LTFU), progression to AIDS and death 48 months after ART initiation was estimated by adjusted Cox regression models. For the second analysis, the mean gain of CD4 cells in the first 24 months following ART initiation was estimated in multivariable linear mixed models.

Results: The first analysis accounted for 12,851 HIV-infected women on ART, from which 1,102 reported at least one pregnancy. After adjustment, pregnancy reduced the risk of AIDS or death (aHR=0.61; 95%CI: 0.40-0.92) and the risk of becoming LTFU at M48 (aHR=0.74; 95%CI: 0.60-0.92). Overall 20,408 HIV-infected women accounted for the second analysis. The mean gain of CD4 cells between ART initiation and M24 was significantly higher among women who experienced a pregnancy in the first six months following ART initiation, compared to those with no pregnancy.

Conclusion: In West Africa, pregnancy post-ART initiation is a common event and reduces by roughly one third the risk of AIDS or death and the risk of LTFU. Moreover, pregnancy post-ART initiation had no deleterious impact on immune response of women initiating ART for their own health.

Keywords: HIV – Pregnancy – ART – Death – Loss to Follow-up – Immune response

Introduction

HIV infection has been pointed out as one leading indirect cause of maternal mortality in the developing world, responsible of 90% of all maternal deaths in sub-Saharan Africa(24, 191, 265-267). The probability of developing potentially fatal HIV-comorbidities increases importantly during pregnancy (9, 18, 268) and the risk of mortality due to maternal causes is eight times higher among HIV-infected pregnant women compared to their uninfected counterparts (24). Additionally, according to several studies pregnancy is not an uncommon event after antiretroviral therapy (ART) initiation and its occurrence increases steadily and proportionally to time on ART, suggesting that the outstanding improvement of health status owed to ART, might also restore fertility functions among HIV-infected women(209, 226, 227, 269).

Current evidence on the relationship between pregnancy and the health status of HIV-infected women on ART is somewhat contradictory. Becoming pregnant after ART initiation was associated with a decreased risk of death or AIDS-related clinical events among South African women (242), contrasting with findings in Uganda where pregnancy and postpartum period were independent risk factors for death among HIV-infected women initiating ART, particularly during the early ART period(248).

As fetal tissues might be highly antigenic, pregnancy is considered a major challenge for maternal immune system. Thus in order to successfully take the pregnancy to full-term, maternal immune system must provide a maternal-fetal tolerance state which is characterized by important central and peripheral changes of maternal immunity(270-273). Thus, in order to control the production of new potentially fetus-reactive T cells, maternal thymus reduces its size and changes its histological structure(274). Additionally, maternal tolerance system is completed by a subtle balance of cytokines Th1-Th2, favored by former histological changes (275, 276). Recent evidence points out that pregnancy do not affect adversely the immunologic course of HIV infection (273). However, we can hypothesize that the time when pregnancy occurs might influence long-term immunological recovery of HIV-infected women on ART and the clinical course of HIV disease once in care.

While the increasing incidence rate of pregnancy post-ART initiation in sub-Saharan Africa, scientific evidence is well documented the impact of pregnancy on mother's HIV-infection while on ART is less well investigated, particularly in West-Africa. We aimed at estimating the pregnancy related-risk of AIDS-disease progression, death or loss to follow-up among HIV-infected women of reproductive age on ART in eight West-African countries. We aimed at estimating the gain of CD4 cells according to time of pregnancy after ART initiation within the same population.

Methods

The IeDEA West Africa collaboration

The International epidemiological Database to Evaluate AIDS (IeDEA) initiative (http://www.iedea-hiv.org) is a consortium of leading clinicians and epidemiologists launched in 2006 that has been addressing high priority research questions and streamline HIV/AIDS research through large pooled regional databases. Its African organization was extensively described elsewhere (277). This cohort analysis was conducted within the IeDEA West Africa Collaboration (http://mereva.isped.u-bordeaux2.fr/iedea/Accueil.aspx). Fifteen HIV/AIDS adult clinics located within eight countries were eligible for in this analysis: Benin (n=1), Burkina Faso (n=2), Côte d'Ivoire (n=5), Gambia (n=1), Guinea Bissau (n=1), Mali (n=2), Nigeria (n=2) and Senegal (n=1). The data collected capture demographic, clinical, biological and therapeutic information at baseline and during follow-up visits. Every 18 months, each cohort submits information to the central coordinating center, using a standardized data format.

Inclusion/exclusion criteria and study sample

We conducted a retrospective analysis within the West-African cohort database among all HIV-infected women of reproductive age (<50 years old), ART-naïve and starting ART between January 1998 and December 2011 under the clinical criteria established by the in-country ART protocols. Women meeting following criteria were not retained for the main analyses: 1) All women reported as previously exposed to ART for prophylaxis purposes (prevention of MTCT); 2) All women with a positive pregnancy status at ART start even if they were meeting clinical criteria to start treatment and; 3) All women not reporting any follow-up visit after ART initiation. Finally, one clinic participating of the consortium was not documenting pregnancies systematically within its database and therefore was not taken into account.

Statistical analysis

Baseline characteristics of study population were described and compared using Kruskal-Wallis test and Chi square test for continuous and categorical variables respectively. In order to address our research questions two different methods used.

Pregnancy related-risk of AIDS-disease progression, death or loss to follow-up

The risk of AIDS disease progression, death and loss to follow-up over 24 months of follow-up was estimated using Cox regression models were pregnancy was considered as a time-dependent variable. To estimate the pregnancy-associated risk two models were proposed: 1) the first model considered that the pregnancy-associated risk period was of 15 months from pregnancy detection; 2)

The second model considered the pregnancy-associated risk period since pregnancy detection and for the following 24 months. In order to control the potential confusion bias, women starting ART at AIDS clinical stage III or IV were excluded from this analysis.

We also ran three additional models to test sensitivity of previous survival analyses: In the first of them, all women starting ART at an advanced AIDS clinical stage were withdrawn; in the second one, besides withdrawing women starting ART at an advanced AIDS clinical stage, we included all women starting ART while pregnant. Finally, one last sensitivity model was conducted were all women were taken into account, regardless of their health or pregnancy status at ART initiation.

Estimation of the gain of CD4 cells according to time of pregnancy after ART initiation

Immunologic response to ART was modeled with linear mixed models (LMM). CD4 cell count change was modeled within a 24 months period starting at ART initiation. The LMM had no intercept and two slopes, the first slope within the first 6 months after starting ART and the second slope between 6 and 24 months after ART initiation. The LMM was adjusted for initial CD4 count, pregnancy, age at ART initiation, first ART regimen, and calendar year of ART initiation, Body Mass Index (BMI), baseline hemoglobin and country. For this analysis, only women having a documented CD4 cell count at ART start were retained. To take into account intra-individual correlation of the repeated CD4 count measures, we performed random effects on the two slopes with a diagonal variance-covariance matrix structure. To verify the adequacy of the multivariable LMM, residual homoscedasticity and normality of the random effect were graphically verified.

Results

Retention in care and risk AIDS-disease progression or death

Study sample

As shown in **figure 1**, overall 12,851 (8.6%) HIV-infected women on ART accounted for the survival analysis out of who 1,102 women reported at least one pregnancy after ART initiation. As shown in **table 1**, women who became pregnant after ART initiation were significantly younger at ART start than women who did not (29.5 years old, IQR:[26.5-32.8] Vs. 33.4 years old, IQR:[28.8-39.2]; p<0.001).

Median CD4 cell count at ART initiation among women who became pregnant was significantly lower compared to those who never became pregnant during this period (199, IQR:[122-307] Vs. 189, IQR:[105-285], p<0.001); 38,2% of women who became pregnant after ART initiation started ART with CD4 levels >200 cells and 34.0% of the other group (p=0.01). Although median hemoglobin at ART initiation was not significantly different among the two groups of women, women becoming

pregnant after ART start had more frequently higher levels of hemoglobin at ART initiation than those who didn't (p=0.004).

Pregnancy was more frequent among women who started ART with a Nevirapine-based regimen than among those starting with a different ART regimen (82.6% Vs. 70.1%; p: <0.001). Although not statistically significant, death rate was significantly lower among women who did not report any pregnancy after ART start compared to those who reported a pregnancy after ART initiation(1.5% Vs. 2.3%; p: 0.06).

After adjustment on baseline CD4 cell count, age, BMI, hemoglobin at ART initiation, initial ART regimen, calendar year at ART start and country, the first model restricting pregnancy-associated hazard risk period at 15 months from pregnancy detection, even if not statistically significant, the fact of becoming pregnant after ART initiation didn't increase the risk of progressing to AIDS and/or to clinical stages III,IV or dying (aHR: 0.61, 95% confidence interval: [0.40 – 0.92], p: 0.01). Similarly, the risk of becoming lost to follow-up was lower in case of pregnancy after ART initiation (aHR: 0.74, 95% Confidence interval: [0.60 – 0.92], p<0.001). Finally, becoming pregnant after ART initiation reduced the risk of all three outcomes combined (aHR: 0.74, 95% Confidence Interval: [0.61-0.90], p=0.003). **(Table 2)**

In the second model, considering pregnancy-related hazard risk period at 24 months since pregnancy detection were similar to first model. After adjusting on the same variables, the risk of AIDS disease progression and/or clinical stages III,IV or death was lower in case of pregnancy (aHR: 0.63, 95% Confidence Interval: [0.42 – 0.96], p=0.03). As the first model, the risk of becoming lost to follow-up at 24 months was lower for women who reported a pregnancy after ART initiation (aHR: 0.73, 95% Confidence Interval: [0.59 – 0.91], p<0.001). Finally, pregnancy post-ART initiation lowered the risk of all three outcomes combined at 24 months (aHR: 0.70, 95% confidence interval: [0.58 – 0.86], p<0.001) **(Table 2)**

Sensitivity analyses

In order to ascertain results of main survival analyses, we ran three sensitivity survival models (results not shown). Firstly, we ran the same models excluding all women starting ART already at an advanced clinical stage (stages C/III, IV), it appeared that whether the pregnancy-related risk period was restricted to 15 months after pregnancy detection or beyond; pregnancy remained associated to a reduced risk of death, AIDS disease progression and becoming lost to follow-up. Compared to the main survival model, the hazard ratios observed a slightly decrease but all of them reached a statistically significant threshold. Additionally, we ran a second model on the same population as the

former one, but this time including all women with a positive pregnancy status at ART initiation and pregnancy remained positively and significantly associated with a reduced hazard risk of AIDS disease progression, LTFU or both outcomes combined when the risk period was of 24 months. Although pregnancy remained associated with a reduced hazard risk for all three outcomes at 15 months, the association with AIDS-disease progression lost it significance. Finally, we ran a model taking into account all women of reproductive age regardless neither their clinical stage nor their pregnancy status at ART initiation. The results of this last sensitivity analysis appeared to be similar to the main survival models, pregnancy remained associated with a reduced risk of death, AIDS disease progression or becoming loss to follow-up.

Immune response according to time of pregnancy after ART initiation

Study sample

As shown in **figure 2**; overall, 20,408 HIV-infected women on ART accounted for the linear mixed model analysis. Within this population sample, 1,615 women reported at least one pregnancy post-ART initiation during the period analyzed. Women becoming pregnant were significantly younger at ART initiation than those who did not (29.5 years old, IQR:[26.3 – 32.7) Vs. 33.4 years old, IQR:[28.8-39.4], P<0.001).

Among women becoming pregnant, median CD4 levels at ART initiation were significantly higher than among those who never became pregnant (189 cells/mm^3, IQR: 105-282) Vs. 169 cells/ mm^3, IQR:[82 – 264, p<0.001). Likewise, women becoming pregnant appeared to have better clinical HIV status at ART start and those who never became pregnant during the period of the study were more likely to be at clinical stages C/III,IV (24.5% Vs. 18.7%).

Median hemoglobin level was slightly different between the two groups of women (10.2 gr/dl, IQR: [9.0-11.4] Vs. 10.1 gr/dl, IQR:[8.8-11.3], p0.007). Similarly, women becoming pregnant were more likely to start treatment with a Nevirapine-based regimen than those who never became pregnant (74.7% Vs 64.0%, p<0.001). Finally, death rate was significantly higher among women who never became pregnant than among those becoming pregnant (1.5% Vs. 4.3, P<0.001). **(Table 3)**

The fully adjusted model showed that mean gain of CD4 cells among women becoming pregnant within the first six months was significantly higher than among those who didn't. Even if not statistically different this gain remains slightly higher among those who became pregnant six months and 12 months after ART initiation. Finally at 24 months, our estimations pointed out a higher mean gain of CD4 cells for women who became pregnant during the first six months after ART initiation and this gain is statistically significant **(Table 4)**.

Discussion

According to our findings, pregnancy after ART initiation seems to be associated to a lower risk of death or AIDS disease progression at 24 months among HIV-infected west-African women. Although this association appeared not to be statistically significant when the risk period was restricted to 15 months from pregnancy detection; at 48 months, this protective association finds statistical significance. Our findings showed as well that the risk of becoming lost to follow-up decreased significantly among women who became pregnant post ART initiation whether the risk period is of 15 months or 48 months after pregnancy detection.

To our knowledge this is the first study estimating pregnancy-related risk of death, AIDS disease progression or loss to follow-up in west-Africa. In contrast with our findings, *Matthews L et al(248)* reported recently that among HIV-infected Ugandan women, the pregnancy-related risk of dying after ART initiation was high during pregnancy and postpartum (aHR: 21.48, 95% CI: 3.73–123.51), although decreasing proportionally to the time on ART follow-up, it remained positively associated and statistically significant. On the other hand, our findings remain consistent with those of *Westreich et al(242)* in South Africa, suggesting that besides pregnancy post-ART initiation is not associated with a higher risk of disease progression or death; it might be a protective factor for HIV-infected women.

A major strength of our findings is the fact that IeDEA West Africa dataset contains socio-demographic and clinical information of a large number of HIV-infected patients on ART, followed-up for over ten year across eight West-African countries. As our analyses were conducted on a retrospective dataset, we were only able to control a limited number of potential confounders. This applies particularly to plasma viral load, marker of treatment adherence and response.

As pregnancy is not systematically detected during clinical visits we suspect an important number of pregnancies have gone unnoticed. In addition, variables enabling to accurately estimate a pregnancy-related risk period such as gestational age at pregnancy detection, delivery date and pregnancy outcome are frequently unavailable. As we believe it is important to differentiate crude and maternal mortality, we estimated our hazard ratios on a shorter risk period (15 months) as a proxy of maternal mortality risk and a longer one (24 months), although still short, as a proxy of overall mortality.

Of note, within our dataset an important number of women are declared lost to follow-up but as the verification of vital status of these women is not exhaustive and some of them might have passed away or just transferred to another health facility, we believe that the death rate estimation within our sample might be biased, we decided therefore to estimate the risk of a combined outcome death

and AIDS disease progression. Furthermore, we conducted several sensitivity analyses which remained consistent with our primary findings.

Regarding CD4 cells count evolution over the time, our findings point out that the CD4 cells gain at 24 months after ART initiation was significantly higher among women becoming pregnant during the first six months after ART initiation compared to those never becoming pregnant or those who became pregnant later. We hypothesize first that pregnancy-related peripheral T cells expansion might concern CD4 cells which, among women becoming pregnant during early ART initiation (<6 months), coincide with rapid CD4 cells release of CD4 cells stocked in the thymus, characteristic of early post-ART period. Moreover, pregnancy during early ART might be an extra stimulation of this rapid release, taking women who became pregnant during early post ART to a higher sustained plateau level of CD4 cells, lead to a higher long-term gain of CD4 cells. However, as women who became pregnant had an improved health status at ART initiation when compared to those who never did, higher CD4 cell count at ART initiation might have favored a higher gain of CD4 cell counts at the end of the study period.

Our second hypothesis is behavioral and suggests that these three groups of women might have different adherence profiles. Adherence to ART among HIV-infected women becoming pregnant during early stages after ART initiation might be more optimal owed to the recent exposure to therapeutic education provided more frequently and intensively in conjunction with prenatal clinical visits. Moreover, HIV-infected women becoming pregnant during early stages after ART initiation are maybe more exposed to therapeutic education underlying the importance of adherence not just for her health but to prevent mother to child transmission as well.

This second analysis was conducted on immunological response within a large sample of HIV-infected women, meeting strict inclusion criteria and relying on an important number of CD4 cell measures. We were able to control on an important number of variables to limit confounders. Also, the robustness of linear mixed model method allowed to control on missing data. However, whether these variations of immunological response are due to biological factors, behavioral factors or a combination of both, merits further research. Moreover, we restrained our analyses to a 24 months period because of data availability but we suspect that pregnancy might have an impact on immune response beyond this period and this merits further research. Although not definitive, these findings suggest that pregnancy post ART initiation may play a role on immune recovery dynamics, leading possibly to important clinical consequences.

In summary, according to our findings, becoming pregnant after ART initiation was associated with lower risk of death or HIV disease progression among HIV-infected West-African women of

reproductive age. Additionally, pregnancy after ART start appeared to be associated to a reduced risk of becoming lost to follow-up. Our findings are consistent with those from other observational cohorts in other sub-Saharan African settings. Finally, immunological response might be mediated by a combination of biological and behavioral factors; metabolic changes yielded by hormonal activity during pregnancy and adherence to ART during this period might have repercussions on CD4 cells evolution of HIV-infected women on ART. In order to better manage pregnancy post-ART initiation more research is needed to fully understand the role of pregnancy in the CD4 cell evolution dynamics and its determinants.

In conclusion, HIV-infection has been pointed out as one major indirect cause of maternal mortality and it is indeed a very challenging event for maternal immune system, the correct management of HIV-infected pregnant women in order to assure mother's health is of high clinical and public health concern.

Tables & Figures

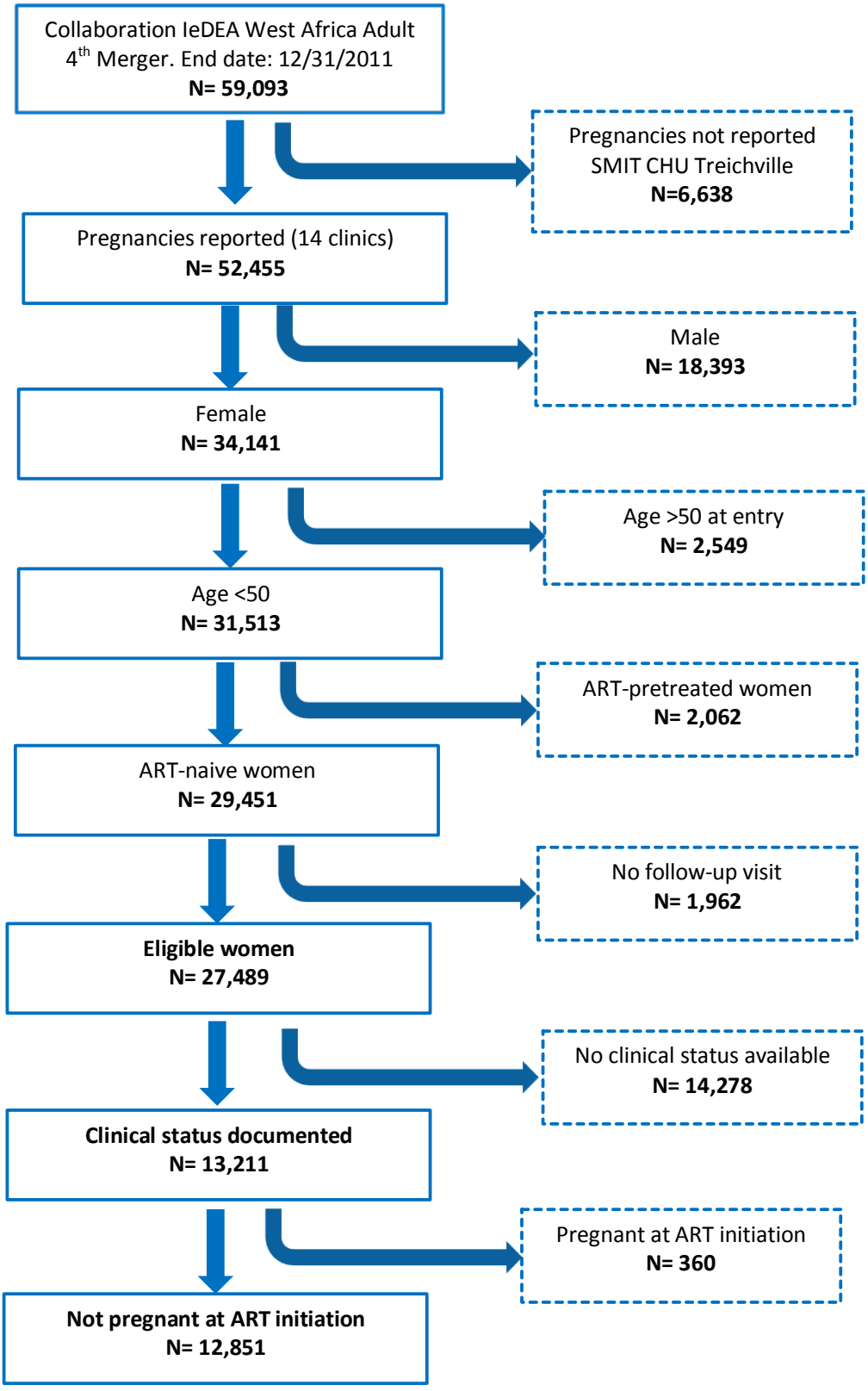

Figure 1. Flow chart survival analysis – the IeDEA West Africa collaboration

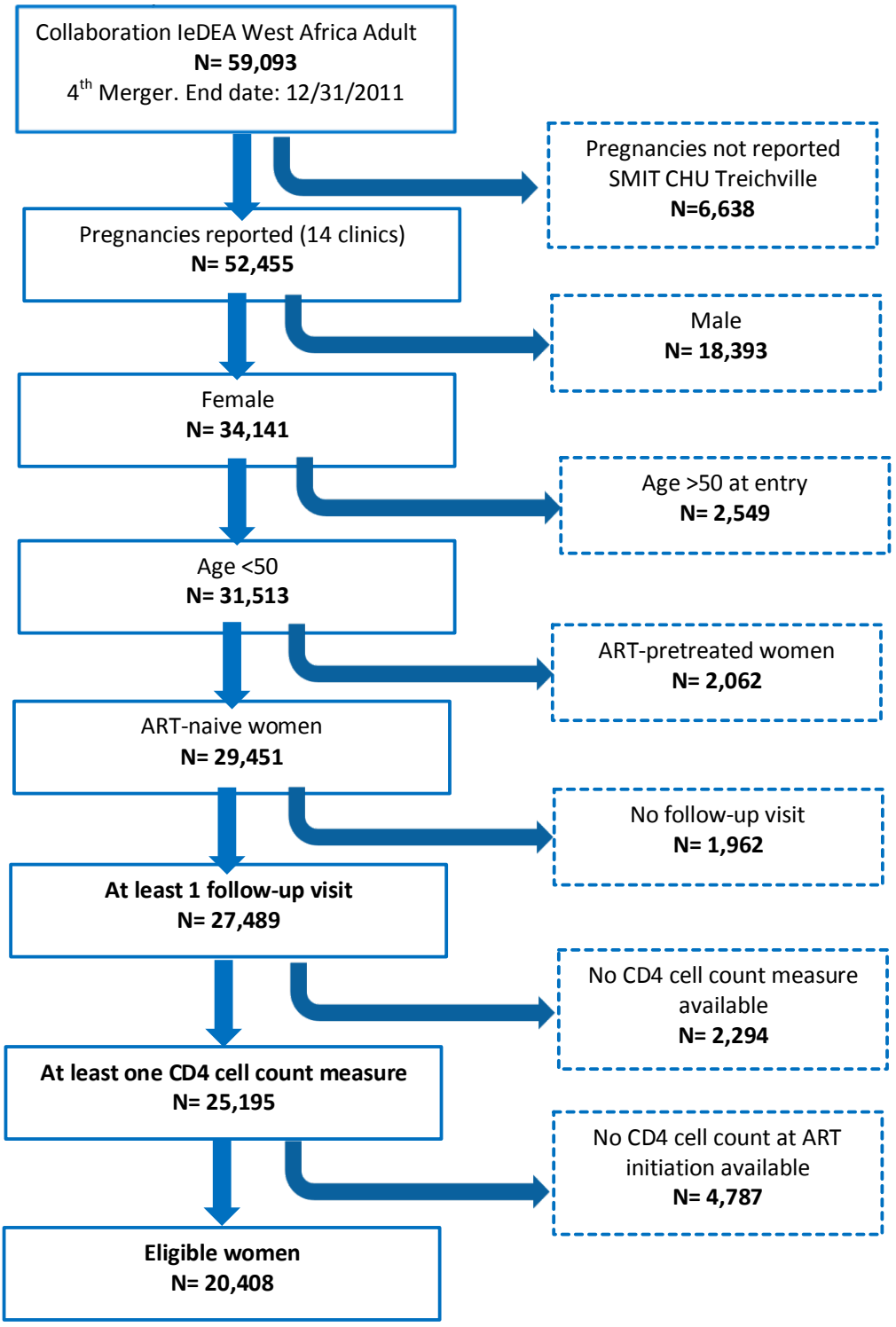

Figure 2. Flow chart linear mixed model – the IeDEA West Africa collaboration

Table 1. Baseline characteristics of eligible women for survival analysis (n=12,851). IeDEA West Africa Collaboration.

Variables	Pregnant women (n=1,102)	Not pregnant women (n=11,749)	Total (n=12,851)	p-value
Median age in years (IQR*)	29.5 (26.5;32.8)	33.4 (28.8;39.2)	32.9 (28.5;38.6)	<0.0001**
Median CD4 count in cells/µl (IQR)	199 (122;307)	189 (105;285)	190 (106;287)	0.0011**
CD4 count in categories (%):				0.0116£
<50 cells/µl	78 (7.1)	1,003 (8.5)	1,081 (8.4)	
50-99 cells/µl	81 (7.4)	1,010 (8.6)	1,091 (8.5)	
100-199 cells/µl	263 (23.9)	2,574 (21.9)	2,837 (22.1)	
200-349 cells/µl	268 (24.3)	2,717 (23.1)	2,985 (23.2)	
>349 cells/µl	153 (13.9)	1,275 (10.9)	1,428 (11.1)	
Missing	259 (23.5)	3,170 (27.0)	3,429 (26.7)	
Median hemoglobin in g/dl (IQR)	10.5 (9.4;11.5)	10.5 (9.2;11.6)	10.5 (9.2;11.6)	0.2416**
Hemoglobin in categories (%):				0.0046£
<7.5 g/dl	30 (2.7)	419 (3.6)	449 (3.5)	
7.5-10 g/dl	210 (19.1)	2,071 (17.6)	1,311 (10.2)	
10-12 g/dl	343 (31.1)	2,742 (23.3)	3,085 (24.0)	
≥12 g/dl	117 (10.6)	1,194 (10.2)	2,281 (17.8)	
Missing	402 (36.5)	5,323 (45.3)	5,725 (44.6)	
First ART regimen (%)				<0.0001£
2NRTIs†+nevirapine	910 (82.6)	8,241 (70.1)	9,151 (71.2)	
2NRTIs+efavirenz	101 (9.2)	2,477 (21.1)	2,578 (20.1)	
2NRTIs+PI‡	61 (5.5)	726 (6.2)	787 (6.1)	
3NRTIs	13 (1.2)	170 (1.5)	183 (1.4)	
Others	17 (1.5)	135 (1.2)	152 (1.2)	
Deaths 5 years after ART (%)	16 (1.5)	273 (2.3)	289 (2.3)	0.0620£

*IQR: Interquartile Range

† NRTI: Nucleoside Reverse Transcriptase Inhibitor

‡ PI: Protease Inhibitor

Table 2. Effect of pregnancy (time dependent variable) on loss to follow-up, AIDS progression and death at 48 months after ART initiation, estimated by adjusted Cox regression model (N=12,851). IeDEA West Africa Collaboration.

	Adjusted Hazard Ratio†	95% CI	p-value
***Model 1: Restricted risk period** *			
AIDS or death	0.61	[0.40-0.92]	0.01
Lost to follow-up	0.74	[0.60-0.92]	0.006
Both	0.74	[0.61-0;90]	0.003
***Model 2: Unrestricted risk period** **			
AIDS or death	0.63	[0.42-0.96]	0.03
Lost to follow-up	0.73	[0.59-0.91]	<0.001
Both	0.70	[0.58-0.86]	<0.001

* Restricted risk period: risk period starts at pregnancy reporting date and goes until 15 months after pregnancy detection.

** Unrestricted risk period: risk period starts at pregnancy reporting date and goes endpoint date (e.g. maximum 48 months after ART initiation).

† Adjusted on CD4 count at baseline; age, Body Mass Index (BMI) and hemoglobin at ART initiation; initial ART regimen; calendar year of starting ART and country.

Table 3. Baseline characteristics of eligible women for linear mixed models for CD4 trayectory. IeDEA West Africa Collaboration (n=20,408)

Variables	Pregnant women (n=1,615)	Not pregnant women (n=18,793)	Total (n=20,408)	p-value
Median age in years (IQR*)	29.5 (26.3;32.7)	33.4 (28.8;39.4)	33.0 (28.5;38.8)	<0.0001**
Median CD4 count in cells/µl (IQR)	189 (105;282)	169 (82;264)	170 (84;266)	<0.0001**
CD4 count in categories (%):				<0.0001£
<50 cells/µl	186 (11.5)	3,082 (16.4)	3,268 (16.0)	
50-99 cells/µl	187 (11.6)	2,534 (13.5)	2,721 (13.3)	
100-199 cells/µl	495 (30.7)	5,491 (29.2)	5,986 (29.3)	
200-349 cells/µl	512 (31.7)	5,412 (28.8)	5,924 (29.0)	
>349 cells/µl	235 (14.6)	2,274 (12.1)	2,509 (12.3)	
Clinical stage (%):				<0.0001£
A,B/I,II	1,146 (71.0)	11,920 (63.4)	13,066 (64.0)	
C/III,IV	302 (18.7)	4,597 (24.5)	4,899 (24.0)	
missing	167 (10.3)	2,276 (12.1)	2,443 (12.0)	
Median hemoglobin in g/dl (IQR)	10.2 (9.0;11.4)	10.1 (8.8;11.3)	10.1 (8.9;11.3)	0.0073**
Hemoglobin in categories (%):				0.0016£
<7.5 g/dl	85 (5.3)	1,281 (6.8)	1,366 (6.7)	
7.5-10 g/dl	477 (29.5)	5,453 (29.0)	5,930 (29.1)	
10-12 g/dl	583 (36.1)	5,724 (30.5)	6,307 (30.9)	
≥12 g/dl	191 (11.8)	2,107 (11.2)	2,298 (11.3)	
Missing	279 (17.3)	4,228 (22.5)	4,507 (22.1)	
First ART regimen (%)				<0.0001£
2NRTIs†+nevirapine	1,207 (74.7)	12,019 (64.0)	13,226 (64.8)	
2NRTIs+efavirenz	266 (16.5)	5,097 (27.1)	5,363 (26.3)	
2NRTIs+PI‡	97 (6.0)	1,225 (6.5)	1,322 (6.5)	
3NRTIs	14 (0.9)	218 (1.2)	232 (1.1)	
Others	31 (1.9)	234 (1.3)	265 (1.3)	
Deaths 5 years after ART (%)	24 (1.5)	811 (4.3)	835 (4.1)	<0.0001£

*IQR: Interquartile Range

† NRTI: Nucleoside Reverse Transcriptase Inhibitor

‡ PI: Protease Inhibitor

£ Global P-value

Table 4. CD4 count cells gain in the first 24 months following antiretroviral therapy (ART) initiation estimated by adjusted* linear mixed models (n=20,408). IeDEA West Africa Collaboration

	Mean CD4 count slope between ART initiation and M6 (cells/µl gained per month)		***Mean CD4 count slope between M6 and M24 (cells/µl gained per month)***		***Mean CD4 count gain between ART initiation and M24 (cells/µl)****	
Variables	***Adjusted estimate** (95%CI)***	***p-value***	***Adjusted estimate** (95%CI)***	***p-value***	***Adjusted estimate** (95%CI)***	***p-value***
No pregnancy	+29.9 (26.6;33.3)	Ref	+5.6 (2.5;8.7)	Ref	+280 (227;333)	Ref
Pregnancy in the first 6 months after ART initiation	+35.5 (31.6;39.4)	<0.0001	+5.7 (2.5;8.8)	0.7839	+315 (260;370)	<0.0001
Pregnancy beyond 6 months after ART initiation	-	-	+5.7 (2.5;8.8)	0.7839	+281 (227;335)	0.7839

* Linear mixed models adjusted for CD4 count at baseline; age, Body Mass Index (BMI) and hemoglobin at ART initiation; initial ART regimen; calendar year of starting ART and country.

** For the reference group: baseline CD4 count <50 cells/µl, 16-24 years old women treated with nevirapine, starting ART in 2011, with BMI=18.5;25kg/m², baseline hemoglobin<7.5g/dl and followed-up in Côte d'Ivoire.

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11. Final discussion

The original research included within this doctoral research framework is probably among the firsts addressing the subject of reproductive health among HIV-infected women on antiretroviral treatment in West Africa under a multidisciplinary quantitative approach. Studying the subject of reproductive health among HIV-infected women on antiretroviral treatment under a psychosocial, epidemiologic and clinical approach, is an important strength of the present doctoral research framework.

Moreover, as the vast majority of similar existing scientific evidence on reproductive health of HIV-infected women on antiretroviral treatment belongs mostly to East and Southern Africa, the present original scientific research fulfills important scientific knowledge gaps about this subject in the West African region. It is worth to note that during my literature search it seemed to me that the existing epidemiologic information of the West-African's HIV epidemic is somewhat dearth. Anyhow, even if available epidemiologic information suggests that the West African HIV epidemic presents a less aggressive profile compared to other sub-Saharan Africa regions hosting epidemics of greater magnitude, it followed the same gender trend. Similarly to other sub-Saharan Africa regions, in West Africa, women and girls hold the higher HIV epidemic burden.

In addition, and concerning more specifically the different approaches I found several strengths. Although intimate partner physical and sexual violence is considered a psychosocial phenomenon associated to important negative health outcomes for HIV-infected women, it has been scarcely studied in West Africa. The study aiming at estimating the prevalence rate of intimate partner physical and sexual violence among HIV-infected women in clinical care and its associated factors in Togo, presented within this doctoral research framework is amongst the first conducted in the region.

The findings of this study showed that the prevalence rate of intimate partner physical and sexual violence was globally high but it was strikingly higher among HIV-infected Togolese compared to their uninfected peers. According to our findings for example almost seven out of ten of the HIV-infected Togolese women of our sample were victim of sexual violence perpetrated by her intimate partner. Moreover, our findings showed as well that intimate partner violence has important negative physical consequences for this population.

Concerning the epidemiologic approach, the literature review I conducted suggests that pregnancy is not an uncommon event among HIV-infected women on antiretroviral treatment in sub-Saharan Africa and, probably having important repercussions on HIV-infected women health. Estimations of the incidence rate of pregnancy following the initiation of antiretroviral treatment have been produced by almost every region in sub-Saharan Africa as it is considered an important public health indicator. In West Africa the incidence rate of pregnancy among HIV-infected women on antiretroviral treatment have been scarcely documented.

The second study presented within this doctoral framework is probably the larger aiming at estimating the incidence rate of pregnancy following the initiation of antiretroviral treatment in West Africa. According to our findings, the crude global incidence rate of pregnancy among HIV-infected women on antiretroviral treatment is of 2.96 pregnancies per 100 women-years (95%CI: 2.85 - 3.08), increasing proportionally to time on clinical follow-up. Although these estimations are probably lower than those reported by other sub-Saharan African regions, it remains consistent with their epidemiological trend.

Finally, under a more clinical perspective, I aimed at estimating the pregnancy-related risk of death, HIV-disease progression and loss to follow-up among HIV-infected women on antiretroviral treatment. In sub-Saharan Africa, this particular risk has been estimated within Eastern and Southern African clinical cohorts of HIV-infected women. To my knowledge this is the first study aiming at estimating these outcomes within a large observational cohort of HIV-infected west-African women.

According to our findings, for HIV-infected women, becoming pregnant after starting antiretroviral treatment is not associated with a risk of death or HIV-disease progression. Moreover, our findings point out as well that pregnancy after antiretroviral treatment initiation is associated with a lower risk of loss to follow-up. These findings appeared to be consistent with findings of a similar study conducted in South Africa(242). However, recent findings from a study conducted in Uganda suggest an association in the opposite direction (248). Anyhow, as pregnancy has been associated with impaired virological outcomes among HIV-infected women on treatment(242) and recent research point out HIV-infection as one major indirect cause of maternal death(24), more research is needed to clarify if whether or

not pregnancy is associated with a higher risk of death among HIV-infected women on antiretroviral treatment.

It is noteworthy that, an important additional strength of the studies presented within this research framework is possibility of exploiting a large regional database. IeDEA West Africa observational database encompass sociodemographic and clinical information of a large number of HIV-infected patients on clinical follow-up over a long period of time across nine West African countries.

However, it is important to underscore that even if IeDEA West Africa data base contains a huge amount of clinical information of people living with HIV/AIDS on antiretroviral treatment, these data should maybe be considered of moderate quality. The important number of missing data within this data base limits the analysis, interpretation and extrapolation of findings. Moreover, reproductive health outcomes of HIV-infected women are poorly documented within IeDEA West Africa datasets. Pregnancy is not systematically cataloged within datasets and when cataloged not fully documented. Finally, as IeDEA West Africa observational cohort is more interested in epidemiologic and clinical outcomes, psychosocial data is unavailable.

On the other hand and more related to the major scientific conceptual frameworks several methodological limitations must be disclosed. Although the literature review of the subject was not conducted under a strictly rigorous systematic methodology, I believe that within this research framework I included a large sample of the most recent, sounding and solid scientific evidence on reproductive health and HIV infection in sub-Saharan Africa. Moreover, in order to enrich the view point of my research, in some cases I expanded my search to research studies conducted in industrialized settings. However, I recognize that owed to this methodological limit, I could have missed probably important and sounding scientific evidence not cited within the present scientific framework.

It is worth to note as well that, besides the scientific literature reviewed, I reviewed and included within the present document an important amount of global political statements, strategic frameworks and global action plans which served to frame my research, adding consistency to current global health priorities.

Finally, I believe that the research conducted within this doctoral framework is consistent with the current knowledge needs set out by the global action plans aiming at putting an end to HIV pandemic, particularly those of the global plan of Elimination of New HIV Pediatric Infections and Keeping the Mothers Alive released by UNAIDS in 2011. This consistency with larger global framework, I believe add a special value to the present research and probably makes of its findings key public health inputs for the West African region.

12. Final Conclusion

During last decade, paramount goals have been achieved worldwide in terms of rolling back HIV epidemic. However, I believe that HIV epidemic among women has not been probably correctly addressed and the magnitude of the epidemic among this population was maybe underestimated. The first global action plans lacked probably of more solid, clear and objective gender-based strategies and intervention addressing HIV epidemic among women and girls. This was probably a reason explaining why it took so long to detect the rapid spread of HIV epidemic among women.

Women and girls are at the crossroads of HIV transmission pathways, more vulnerable to acquire HIV infection through sexual intercourses and to transmit the virus to their children through vertical mechanism during pregnancy and/or postpartum. I believe that this particular situation justify the need of more specific public health strategies to prevent the spread of HIV infection among this population. I believe that the design and implementation of women-specific preventive and care strategies might be indeed one important step towards the end of HIV epidemic.

I believe that the higher vulnerability of women to acquire HIV infection is owed to a combination of women-specific biological factors and context-dependent psychosocial factors, interwoven within a dynamic association that needs to be tackled at a structural, societal and individual level. In order to effectively reduce the high epidemic burden of HIV among women, more women-specific preventive interventions addressed at each one of these levels are urgently needed.

The outstanding improvement of health status and life expectancy owed to antiretroviral treatment more HIV-infected women chose to child bear. This is corroborated by the persistent desire of procreation expressed by HIV-infected women and the growing incidence rates of pregnancy estimated following the initiation of antiretroviral treatment. In addition, although HIV-infection has been pointed out as a major cause of maternal death, the pregnancy-related health risks among HIV-infected women are not fully elucidated yet.

I believe that an HIV positive diagnosis is not anymore a contraindication to procreate. However, more scientific evidence is needed to correctly help women living with HIV/AIDS to fulfill their reproductive needs, reducing the associated health risks this could take with for

themselves and their families. Further research must provide with sounding knowledge to design and implement effective motherhood programs for HIV-infected women. These safe motherhood programs should be able to provide assistance on how to prepare the future reproductive program of HIV-infected women desiring to child bear, reducing the risk of sexual transmission; how manage correctly a HIV-positive pregnancy and its associated risks, not only the risk of transmission but the health risks for women themselves. I believe this is one important public health challenge the global community will have to face in a near future.

13. Perspectives

As since the advent of antiretroviral treatment HIV is considered more as chronic manageable disease and pregnancy is not an uncommon event among HIV-infected women on antiretroviral treatment. I believe that there are still important scientific gaps to fully understand the repercussions of pregnancy on health status of HIV-infected women therefore further research on these concerns are of major public health interest.

The fulfilment of these gaps will allow HIV-care programs to correctly address reproductive needs of people living with HIV/AIDS, reduce the potential pregnancy-related risks for HIV-infected women and help HIV-infected individuals desiring to procreate complete their reproductive program reducing the potential associated risks.

Following this thesis of science and in line with my previous work, I expect joining the ***WADA Women & Mothers initiative***, which is a research initiative nested in IeDEA West Africa Observational Cohort. The aim of this initiative is to study the epidemiologic, clinical and psychosocial aspects associated with reproductive health of HIV-infected women on antiretroviral treatment in West Africa.

The research program of this initiative is based on two principal objectives. The first objective is to study the relationship between pregnancies following ART initiation and the health outcomes of HIV-infected women of reproductive age through a multicountry retrospective approach. The second objective is to evaluate the sexual and reproductive health indicators of HIV-infected women on antiretroviral treatment through the design and implementation of a prospective observational cohort (Annex 1).

I believe that the scientific knowledge this initiative will provide will be a key public health input to guide the effective integration of reproductive health services into HIV care services in sub-Saharan Africa. Moreover, I expect as well that this further research will contribute to constitute the foundation of safe motherhood programs for HIV-infected women desiring to child bear as a part of future scale up of HIV comprehensive care services.

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15. Appendix. WADA Women & Mothers Cohort –IeDEA West Africa

Pregnancy intention, incidence and complications after ART initiation and its association with maternal disease progression among HIV-infected west-African women in reproductive age
The WADA-Women & Mothers cohort – IeDEA West Africa

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Version 1.5 – October 2013

1. Scientific background

An estimated 287,000 maternal deaths occurred in 2010 worldwide and 56% of these deaths accounted for sub-Saharan Africa [1]. Moreover, HIV infection is highly prevalent in sub-Saharan Africa, mostly among women in reproductive age. Hence, sub-Saharan Africa is the region with the largest proportion of maternal deaths attributed to HIV infection with 91% of all AIDS-related indirect maternal deaths worldwide occurring in this region, placing HIV-infected pregnant and postpartum women at a risk eight times higher of pregnancy-related death compared to their uninfected counterparts [1-3]. AIDS-related maternal mortality is therefore a major public health concern in sub-Saharan Africa, hindering the achievement of the Millennium Development Goal 4 and 5 by 2015 [1, 4, 5].

Over the last ten years, the generalization of ART implementation has favored a striking improvement of health status among HIV-infected individuals in this region. This outstanding fact, has progressively led to the awakening of childbearing will among HIV-affected couple, increasing procreation desires. Pregnancy after ART initiation is therefore becoming a more and more common event [6-8]. Indeed, several studies have showed that the incidence of pregnancy after ART initiation increases proportionally to years on ART [6, 9, 10].

However, HIV-infected pregnant or postpartum women have a higher risk of pregnancy complications than their uninfected counterparts, such as preeclampsia which is one of the leading direct causes of maternal and fetal deaths [11, 12]. Moreover, HIV-infected pregnant women are particularly more vulnerable to several highly deathful AIDS-related co-morbidities such as bacterial pneumonias, bacterial sepsis and cryptococal meningitis [13]. The risk of developing active tuberculosis, which is the foremost cause of death among HIV-infected individuals, is around ten times higher among HIV-infected pregnant women than among the HIV-uninfected ones [4]. In addition, there is a growing body of evidence that pregnancy after ART initiation has a deleterious impact on maternal immunological response. It has been recently shown in South Africa that pregnancy was associated with a hazard ratio of 1.34 (95% CI 1.02, 1.78), and an estimated absolute 6% increase in virologic failure by five years of follow-up [14].

Such findings suggest detrimental repercussions of pregnancy on HIV-infected women's health, but they are not entirely conclusive. One major limitation of these findings is that they are mostly based on retrospective datasets and/or inadequately powered population samples limiting interpretation. In addition, an important number of pregnancies may go undetected mostly due to unreported miscarriages and abortions, underestimating the real incidence of pregnancy among HIV-infected African women [2, 15, 16]. Similarly, the estimation of the "real" fraction of HIV attributable to maternal deaths is limited by the ineffective linkage between HIV and maternal care services and the subsequent high proportion of loss to follow-up women [2, 16-18].

For the first time, the current global strategy to eliminate HIV mother-to-child transmission (eMTCT) addresses punctually the reduction of maternal mortality as major goal [5]. Past strategies to prevent

HIV transmission from mothers to children focused principally on child health outcomes while HIV is a leading cause of maternal mortality in high prevalence settings. This is an unprecedented opportunity to create safer motherhood programs for HIV-infected women, aimed at keeping them healthy and alive while assuring a new HIV-free generation. Thus definitely, more research is now urgently needed to precisely estimate key strategic indicators on maternal health that will help defining safe motherhood public health policies. This is especially true in west-Africa where both pregnancy incidence and health outcomes among HIV-infected women and mothers are scarcely described. Such crucial information will undoubtedly contribute to the scale-up of eMTCT global plans and to the successful achievement of its main goals within this region.

2. Objectives

We propose the creation of the *WADA Women & Mothers* cohort nested within the IeDEA west-Africa collaboration aimed at answering to the following objectives among HIV-infected women in reproductive age after ART initiation:

- Investigate fertility intentions and identify predicting factors;
- Estimate the incidence and associated factors of pregnancy;
- Estimate the incidence and associated factors of pregnancy complications;
- Investigate the evolution of the immunological response according to incident pregnancies;
- Investigate the association of incident pregnancies with adverse health outcomes: loss to follow-up, AIDS disease progression and maternal mortality.

3. Methodology: Study population, study sites and main outcome measures

Besides standard clinical care data collected within the IeDEA West Africa collaboration, the *WADA Women & Mothers* cohort will prospectively and systematically collect standardized information on women reproductive health and maternal health issues, primarily based on the main outcome measures detailed below. At this stage, it is not possible to adequately answer to the objectives of this proposal using the data routinely collected. We have indeed analyzed in 2013 the data available to estimate pregnancy incidence and understand the association of pregnancy with health outcomes among IeDEA West Africa HIV-infected women (Burgos-Soto et al. Personal communication submitted to CROI 2014, Sept. 2013). These analyses showed a wide variability of pregnancy reporting procedures according to sites leading to underreported and biased estimates. Moreover, key variables like for instance gestational age or pregnancy complications were not collected.

a. Study population

We will constitute a prospective cohort based on both women already in care and women initiating ART:

- All existing HIV-infected women in reproductive age (<49 years) and having initiated ART over the previous two years at the selected clinical sites will be systematically included;
- All pregnant and non-pregnant women newly diagnosed with HIV infection within the selected IeDEA clinical sites and initiating ART (for their own health or as part of a universal ART strategy to prevent mother-to-child transmission of HIV) will be systematically included.

b. Study sites

The *WADA Women & Mothers* cohort will be progressively implemented at five clinical sites of the IeDEA West-Africa collaboration: Ivory Coast (3 clinical sites), Burkina Faso (1 clinical site) and Togo (1 clinical site). Recruitment will take place in two distinct phases over the years 2014 and 2015.

First, recruitment will start in Côte d'Ivoire between January and December 2014. Our choice was based on the fact that Cote d'Ivoire is the country accounting for the largest population of women on ART and the setting with the most developed structural capacity in terms of clinical management and research within the IeDEA West-Africa Consortium. The *WADA Women & Mothers* cohort will be implemented at three clinical sites in the three mostly densely populated districts of Abidjan: the CNTS clinical site in Treichville district, the CEPREF clinical site in the Yopougon district and the Avocatier clinical site in the Abobo district. On the basis of previous estimations of annual recruitment capacities in 2011 and 2012 of the selected clinical sites in Cote d'Ivoire, expected cohort size for its first year is presented in Table 1.

Table 1. Estimated size of the *WADA Women & Mothers* cohort at the end of 2014.

	Women initiating ART in 2012-2013	**Women initiating ART in 2014**	**Total cohort size at the end of 2014**
Côte d'Ivoire - CNTS	286	143	429
Côte d'Ivoire - Cepref	402	201	603
Côte d'Ivoire - Avocatier	156	78	234
Total in Côte d'Ivoire	**844**	**422**	**1,266**

Second, recruitment will continue in Côte d'Ivoire and start in Burkina Faso and Togo between January and December 2015. The *WADA Women & Mothers* cohort will be progressively implemented at two additional clinical sites in rural Burkina Faso (CHU Souro Sanou in Bobo Dioulasso) and urban Togo (CHU Olympo). On the basis of previous estimations of annual recruitment capacities in 2011 and 2012 of the selected clinical sites in Cote d'Ivoire, Burkina Faso and Togo, expected cohort size at the end of its second year is presented in Table 2.

Table 2. Estimated size of the *WADA Women & Mothers* cohort at the end of 2015.

	Women initiating ART in 2013-2014	**Women initiating ART in 2015**	**Total cohort size at the end of 2015**
Cote d'Ivoire (3 sites)	1,266 *	422	1,688
Burkina Faso (1 site)	640	320	960
Togo (1 site)	1,048	524	1,572
Total in the 3 countries	**2,954**	**1,266**	**4,220**

** Women initiating ART in 2012-2014 for Côte d'Ivoire where recruitment will start one year earlier.*

c. Main outcome measures

Fertility intentions (objective #1)

At the time of enrolment, all women will be asked to fulfill a quantitative survey addressing issues related to fertility intentions, unplanned pregnancies and lifetime and current use of contraception methods. An adapted version of the London Measure of Unplanned Pregnancies [19] will be used to assess fertility intentions. This will be completed with qualitative interviews and focus-group discussions on this topic. Moreover, additional socio-demographic, economic, anthropometric (height and weight), family-related and women empowerment characteristics of participating women will be systematically collected in order to complete women's profile characteristics. Family planning counseling will be proposed systematically to all women willing to prevent, stop or space pregnancies and appropriate methods will be proposed according to their will.

Incidence of pregnancy (objective #2)

Incident pregnancies will be detected according to the two following methods:

1. The usual women self-report of pregnancy during clinical follow-up. Every self-report will be confirmed by a urinary or a blood pregnancy test (depending on whether a laboratory assessment was planned for this visit).
2. An anonymous uncorrelated pregnancy urine test will be performed on a 3-monthly basis to every included woman. Urine samples collected to monitor clinical outcomes will be used. Certain non-identifying information will be extracted from the patient's clinical record onto a study form and anonymously linked to each woman. This strategy will produce *gold-standard* pregnancy incidence values for each study site. This will then enable us to estimate to what extent the usual detection method underestimates the actual pregnancy incidence.

Gestational age at pregnancy detection will be systematically assessed on the basis of dates of last menstrual period and/or symphysis-fundal palpation and confirmed through ultrasound

Incidence of pregnancy complications (objective #3)

A control group of women from the general population (e.g. mostly HIV-uninfected given the relatively low prevalence in these countries) will be recruited within maternity wards in each of the three countries to describe epidemiological trends and clinical profile of pregnancy and postpartum complications. For this purpose, every woman from the control group will be matched by age and gestational age to each newly pregnant HIV-infected women of the *WADA Women & Mothers* cohort.

Ultrasound monitoring will be systematically offered for each reported pregnancy to detect anatomical and/or physiological abnormalities of the fetus, placenta, uterus or amniotic sac. Maternal pregnancy complications will be detected through a complete pregnancy evaluation at each antenatal visit and through blood and urine tests systematically performed as soon as the pregnancy is diagnosed, just before delivery and during the early postpartum period.

Hemorrhage is the leading cause of maternal death in developing world and number one in sub-Saharan Africa, accounting for one third of all causes of maternal deaths in this region [17]. The etiology of maternal bleeding is multifactorial and associated causes will depend on the gestational period as shown in the Annex (Figure 1).

All women recruited in the *WADA Women & Mothers* cohort presenting hemorrhage during gestational period are going to be evaluated and treated according to the type of bleeding. Medical staff will report a detailed diagnosis of bleeding and final outcome after management. Severity of bleeding and associated signs and symptoms will be described for each case.

Hypertensive disorders during pregnancy are the second most important contributor to maternal mortality in developing countries, accounting for roughly 9% of all causes of maternal death in sub-Saharan Africa [17]. Amongst all hypertensive disorders associated to pregnancy, pre-eclampsia is one of the deadliest and HIV-infected women on ART are at higher risk to develop this syndrome. Pre-eclampsia is a syndrome characterized by hypertension and renal function impairment [20]. The signs and symptoms characteristics of pre-eclampsia and eclampsia are detailed in the Annex (Figure 2).

Blood pressure will be systematically monitored and documented at every antenatal care visit for all women becoming pregnant during the course of the study. In order to detect the renal function impairment, urine samples will be collected and analyzed (proteinuria and creatinine excretion)at every antenatal visit, during labor and postpartum visits to complete pre-eclampsia screening.

Immunological response and incidence of adverse health outcomes (objectives #3 & 4)

HIV-specific clinical and biological information will be exhaustively collected. CD4 cell counts/percentage (and viral load if available) will be performed following national clinical care protocols. All AIDS-defining events will be systematically reported by midwives at every routine clinical visit. Finally all reported deaths will be verified by midwives, emphasis will be placed to precisely collect the date and circumstances of death through family interviews. An autopsy will be systematically offered to the family of every woman deceasing during the course of the study. Causes of death will primarily rely on this autopsy, or if not performed, on the usual information available.

3. Cohort organization

In order to coordinate logistic aspects, data collection and context-related methodological issues of cohort management, a team of local midwives will be recruited. Owing a vast useful knowledge of local motherhood programs, midwives are key clinical care personnel to participate in the conceptual design of data collection tool adapted to local context specificities and to facilitate the articulation of such a cohort with local maternal health services. One midwife per site will be needed. Additionally, a senior research nurse will be recruited to act as the field project coordinator to ensure standardization of procedures across sites and to be in charge of data quality management. A local data-manager/web-developer will be recruited to create and manage on a day-to-day basis the new data-base specifically dedicated to this cohort. He will also be in charge of progressively implementing a web-based data-collection system for this cohort. Finally, consultancies of gynecologists (for objective #3) and of a social scientist (for objective #1) will also be needed.

Cohort team:

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4. Expected results

With the creation of this women-centered prospective cohort on reproductive health issues, we expect to estimate more precise, bias-less and standardized through sites incidence rate of pregnancy among HIV-infected women in the west-African context. Additionally, identifying region-specific predictors of pregnancy, estimated through reliable methods, will guide political decisions within the west-African region.

Furthermore, on the basis of a prospective follow-up method, we expect to better understand the repercussions of pregnancy on the evolution of immune-virological response among HIV-infected women on ART. We believe that measuring the impact of pregnancy on AIDS disease progression and mortality among HIV-infected women on ART is definitely a major public health priority that is to date not clearly elucidated and scarcely documented within the west-African region. Such an approach also coincides with eMTCT global plan goals.

Moreover, although HIV infection is currently considered one major cause of maternal death in sub-Saharan Africa, more research is needed to understand its role as a direct and indirect cause of maternal death. We expect our results shed more light on this fact, fully describing the epidemiological profile of maternal deaths occurring in this west-African cohort.

Finally, assessing fertility intentions will indubitably become a key input to better address family planning needs among HIV-infected women in reproductive age in West-African region. In this context, the *WADA Women & Mothers* cohort is tailored to enlarging safety motherhood programs for HIV-infected women upon the West-African region

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Annex

Figure 1. Principal causes of hemorrhage according to gestational period [IMPAC] [20].

Early pregnancy Hemorrhage	Antepartum Hemorrhage	postpartum Hemorrhage
• Threatened abortion • Ectopic pregnancy • Complete abortion • Inevitable abortion • Incomplete abortion • Molar pregnancy	• Abruptio placentae • Ruptured uterus • Placenta praevia	• Atonic uterus • Tears of cervix, vagina or perineum • Retained placenta • Retained placental fragments • Inverted uterus • Delayed PPH • Ruptured uterus

Figure 2. Signs and symptoms of pre-eclampsia and eclampsia according to severity (IMPAC) [20].

Mild pre-eclampsia	Severe pre-eclampsia	Eclampsia
• Two readings of diastolic blood pressure 90–110 mm Hg 4 hours apart after 20th week Gestation • Proteinuria up to 2+	• Diastolic blood pressure 110 mmHg or more after 20th week gestation • Proteinuria 3+ or more • Headache (increasing frequency, unrelieved by regular analgesics) • Blurred vision • Oliguria (passing less than 400 mL urine in 24 hours) • Upper abdominal pain (epigastric pain or pain in right upper quadrant) • Pulmonary edema	• Convulsions • Diastolic blood pressure 90mmHg or more after 20th week gestation • Proteinuria 2+ or more • Coma (unconscious) • Other symptoms and signs of severe pre-eclampsia